THE AMERICAN JOURNAL OF Clinical Nutrition

NOVEMBER–DECEMBER 1956 VOLUME 4, NUMBER 6

CONTENTS

VITAMIN E DEFICIENCY IN MAN: BIOCHEMICAL EVIDENCE IN A PATIENT WITH XANTHOMATOUS BILIARY CIRRHOSIS

Calvin W. Woodruff 597

This paper represents what is perhaps the first fully documented report of vitamin E deficiency in man. Careful clinical studies indicate that two laboratory determinations, creatinuria and pentosuria, are useful in defining the metabolic aberration of vitamin E-lack in the human. Other challenging features of what may become a new syndrome are lucidly presented by Dr. Woodruff.

HYPERVITAMINOSIS A. EXPERIMENTAL INDUCTION IN THE HUMAN SUBJECT

Robert W. Hillman 603

This paper reports a unique and important observation. Hypervitaminosis A was induced in a physician. The carefully recorded observations, particularly in relation to the skin, eye, and plasma levels, are important. But of greatest value are the signs, symptoms, and human variability factor so clearly noted in this pioneering paper.

ABSORPTION OF IRON FROM THE GASTROINTESTINAL TRACT

Elaine D. Henley, W. N. Christenson, William J. Grace and Harold G. Wolff. 609

Refined methods for the study of iron metabolism are now available. In this significant report an iron tolerance test, using both stable and radioactive iron, has revealed inaccuracies in the use of serum iron values. The technic described here is more useful and reliable. Furthermore, important data have been accumulated regarding absorption of ferrous and ferric iron, and on iron retention by iron-deficient patients.

PYRUVATE METABOLISM IN OBESITY

A. T. Miller, Jr. and Barbara M. Thomas. 619

The evidence for a metabolic fault in obesity is substantial although the whole picture is not clear. One of the significant areas of dysfunction is said to be pyruvate metabolism. The observations in this valuable study indicate the complexity of the problem.

THE CARE AND NUTRITION OF A PATIENT IN PROLONGED COMA

Ralph L. Hopp, W. J. A. Ford, and S. J. O'Connor. 625

In this remarkable case report, the authors describe their experience in maintaining the nutrition of a patient who has been in coma for 17 months. This is one of the most difficult problems in surgical management, and this report will be of value to all clinicians.

THE NUTRITION OF THE ISOLATED VERTEBRATE CELL

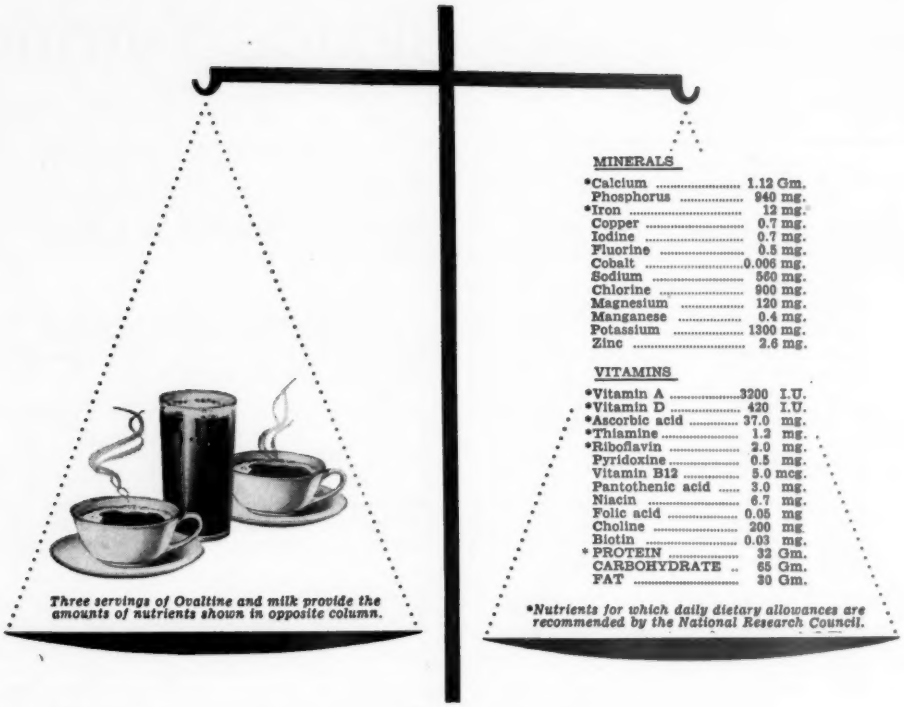
Philip R. White 629

Opening this symposium on "Optimal Nutrition, Its Analysis and Application," Dr. White succinctly presents the problem from the fundamental viewpoint of the tissue culturist. As he so clearly states, optimal nutrition can be a very specific and highly localized affair. Recent *in vitro* work indicates that the surface of this potentially significant field has hardly been scratched. Small changes even in the buffer concentration can have spectacular effects on tissue growth. From such observations as are presented here will come knowledge with the widest implications.

A CONCEPT OF OPTIMAL NUTRITION

W. A. Krehl 634

In a thoughtful and stimulating review of the concept of "optimal" nutrition, Dr. Krehl shows how the principle of homeostasis can be aptly applied to this challenging problem. He points out a working definition and indicates the ramifications of optimal nutrition in all branches of clinical medicine.



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THE AMERICAN JOURNAL OF Clinical Nutrition

NOVEMBER–DECEMBER 1956 VOLUME 4, NUMBER 6

Contents continued from page iii

SOME RECENT DEVELOPMENTS IN ORAL FEEDINGS FOR OPTIMAL NUTRITION IN BURNS

Curtis P. Artz, Harry S. Soroff, Elinor Pearson and Robert P. Hummel 642

The practical application of nutrition is most clearly seen in surgical management. In this interesting presentation, the Army Surgical Research Unit points out the specific details in the nutritional management of the burned patient. Highly useful practical advice regarding protein supplementation is given.

THE DIAGNOSIS OF MALNUTRITION IN WELL-NOURISHED COMMUNITIES

A. M. Thomson 647

In this admirable essay, the author discusses the important and practical subject of the assessment of good health, i. e., good nutrition. Some recent world-wide experiences in matters of growth and health form a valuable background to the appreciation of human variability, seen so clearly in clinical nutrition.

THE RELATIONSHIP BETWEEN POTASSIUM UTILIZATION AND NITROGEN BALANCE

Laurence E. Frazier, Randolph H. Hughes, and Paul R. Cannon. 655

Metabolic research has indicated the interrelationship between nitrogen and potassium. In this lucid study, Dr. Cannon and his associates investigated the utilization of potassium under conditions of tissue anabolism and catabolism. Since all organic disease involves catabolism and all recovery involves anabolism, these observations are of fundamental importance. The finding that potassium utilization was dependent upon position nitrogen balance has, of course, clear clinical implications.

OPTIMAL NUTRITION CORRELATED WITH NITROGEN RETENTION

James B. Allison. 662

In this useful survey Dr. Allison correlates the "labile protein stores" with their responses to various nutritional stresses and discusses the many factors involved in evaluating the significance of nitrogen balance. Cases of tumor growth, particularly, may show a dissociation in balance between various tissues. Important implications for future tumor studies are indicated which involve methionine, riboflavin, pantothenic acid, and a general growth-depressor (TEPA).

POSTABSORPTIVE UNDULATIONS AND OSCILLATIONS IN BLOOD GLUCOSE

George E. Anderson, Robert W. Hillman, Izak F. A. Van Elk and A. John Perfetto. . 673

A new concept is introduced in this well-documented study by Dr. Anderson and his associates. Using a meticulous technic it is possible to show that the blood sugar is in a constant state of flux as various endocrine and nutritional factors participate in maintaining homeostasis. Our understanding of diabetes will be particularly widened as this problem is studied.

EDITORIAL

ANTIBIOTICS PLUS? Charles S. Davidson 687

REVIEWS OF RECENT BOOKS 689

ABSTRACTS OF CURRENT LITERATURE: Energy Requirements in Man; Nutrition Projects and Surveys; Pyridoxine; The Sprue Syndrome; Carbohydrate Metabolism; New Studies on Serum Lipids; Items of General Interest. 691

TABLE OF CONTENTS, VOLUME 4 709

INDEX, VOLUME 4 713

a peptic ulcer patient ...comfortable...well fed...**on the job!**

THE AMERICAN JOURNAL OF Clinical Nutrition

NOVEMBER–DECEMBER 1956 VOLUME 4, NUMBER 6

Vitamin E Deficiency in Man:

BIOCHEMICAL EVIDENCE IN A PATIENT WITH XANTHOMATOUS BILIARY CIRRHOSIS

By CALVIN W. WOODRUFF, M.D.*

NO CLINICAL syndrome directly attributable to a deficiency of vitamin E has been recognized in the human, although low levels of tocopherol in the blood have been noted in sprue[1] and microscopic pigmentation of the muscles has been recorded in this disease.[2,3] The specific biochemical and pathologic changes in experimental animals depleted of this vitamin are well documented. This is a report of several of the biochemical changes characteristic of experimental avitaminosis E which have been observed in a human patient; furthermore, the reversal of some of them following tocopherol therapy has been demonstrated.

METHODS OF STUDY

The tocopherol nutriture of the patient here reported has been evaluated as follows: serum total tocopherol levels were determined by the micromethod of Quaife, Scrimshaw, and Lowry;[4] urinary creatine and creatinine were determined by standard methods; urinary pentose determinations were performed by the method of Minot, Frank, and Dziewiatowski[5]† hydrogen peroxide hemolysis of red cells was performed according to the procedure outlined by Rose and György[6,7] as modified by Gordon;[8] the assay of tocopherol in subcutaneous tissue was made as described by Quaife and Dju.[9]

CASE REPORT

Mrs. E. A., aged 42 years, was first admitted to Vanderbilt University Hospital‡ in October, 1950, with xanthomatous biliary cirrhosis. She had had jaundice, light colored stools, dark urine, pruritus, and four to six bulky stools daily for five years. Four years before admission another clinic had recorded the findings of an enlarged liver, generalized xanthomatous skin lesions, and a serum cholesterol of 1332 mg per 100 ml. She had been placed on a low fat diet to which she adhered conscientiously. Three years before admission she fractured her left tibia and ambulation was rarely attempted after that time because of weakness. During the few months preceding her admission the weakness increased and abdominal distention was noted. She had had a simple hysterectomy three years previously.

Examination revealed a slightly emaciated

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* Markle Scholar in Medical Science.

This work was supported in part by a grant from the National Vitamin Foundation.

† The analyses were kindly performed by Dr. Ann S. Minot.

‡ This patient was seen initially at the request of Dr. Ralph Larsen.

woman of 42 years whose skin and sclerae were olive-colored. Numerous xanthomatous plaques were widely distributed over her skin. The liver was not palpable but the spleen was enlarged to below the level of the umbilicus. The abdomen was distended with gas and fluid. There was no peripheral edema. The physical examination was otherwise within normal limits. Pertinent laboratory findings are summarized in Table I. Roentgen examination revealed generalized osteoporosis, and healed fractures of the left tibia and the eleventh dorsal vertebra.

Absorption of fat was studied by giving a test meal of 650 ml of homogenized milk containing 200,000 IU of vitamin A and 600 mg α-tocopherol. The resulting chylomicron counts* and vitamin A and tocopherol levels indicate impairment of absorption (Fig. 1). Glucose and vitamin A, in a water-dispersible preparation, appeared to be absorbed normally. The addition of bile salts or emulsification in Tween 80®† had no influence upon the absorption of vitamins A and E from oily preparations.

The absence of measurable tocopherols in the serum was associated with creatinuria and pentosuria as indicated in Figure 2. The patient was given 100 mg of α-tocopherol emulsified in Tween 80 daily. Her low fat, high protein diet was continued. In August, 1951, tocopherol medication was replaced by a placebo of Tween 80 in water. In May, 1951, severe low back pain was present on changing posture and three more compression fractures of lumbar vertebrae were found. In January, 1952, a pathologic fracture of the right femur occurred which healed following immobilization.

In May, 1952, the patient was admitted for further study. Pathologic fractures of several vertebrae evidently occurred during the movement associated with roentgen examination. The intravenous administration of calcium gluconate[10] was associated with a marked initial decrease in urinary phosphorus excretion, followed by an abrupt rise in serum phosphorus and a fall in serum calcium concentrations. This was regarded as evidence of intense compensatory activity upon the part of the parathyroid glands compatible with deficient calcium absorption.* A muscle biopsy was performed. Biochemical tests to evaluate vitamin E nutriture were repeated as indicated in Figure 2. On June 5th, the patient received 250 mg of tocopherol in the form of *d*-α-tocopheryl polyethylene glycol 1000 succinate (tocopheryl PGS)† intramuscularly as a 20

TABLE I

Representative Laboratory Determinations

	Date		
	10/30/50	5/26/52	4/17/54
Hemoglobin—g/100 ml	13.0	10.6	11.0
White blood cell count per cu mm	4,500	3,200	4,400
Prothrombin time—% of normal	63	76	49
Total serum protein—g/100 ml	5.5	6.4	5.5
Serum albumin—g/100 ml	2.6	2.8	1.8
Cephalin flocculation at 48 hours	4+	4+	4+
Thymol turbidity—units	20.0	7.5	11.0
Direct serum bilirubin—mg/100 ml	9.8	12.2	14.3
Total serum bilirubin—mg/100 ml	17.1	20.5	24.3
Serum cholesterol—mg/100 ml	220	155	130
Serum calcium—mg/100 ml	8.5	8.1	8.2
Serum phosphorus—mg/100 ml	2.9	2.5	3.4
Serum alkaline phosphatase—Bodansky units	10.0	15.5	17.3
Serum vitamin A—IU/100 ml	66	—	—
Serum carotene—μg/100 ml	18	—	—
Nonprotein nitrogen—mg/100 ml	26	36	24

* The chylomicron counts were made by Dr. Carl Anderson.

† These emulsions were prepared by Dr. H. C. Meng.

* Dr. Beverly T. Towery's aid in investigating and treating the osteomalacia is gratefully appreciated.

† This preparation was supplied by Dr. Philip L. Harris of Distillation Products Industries.

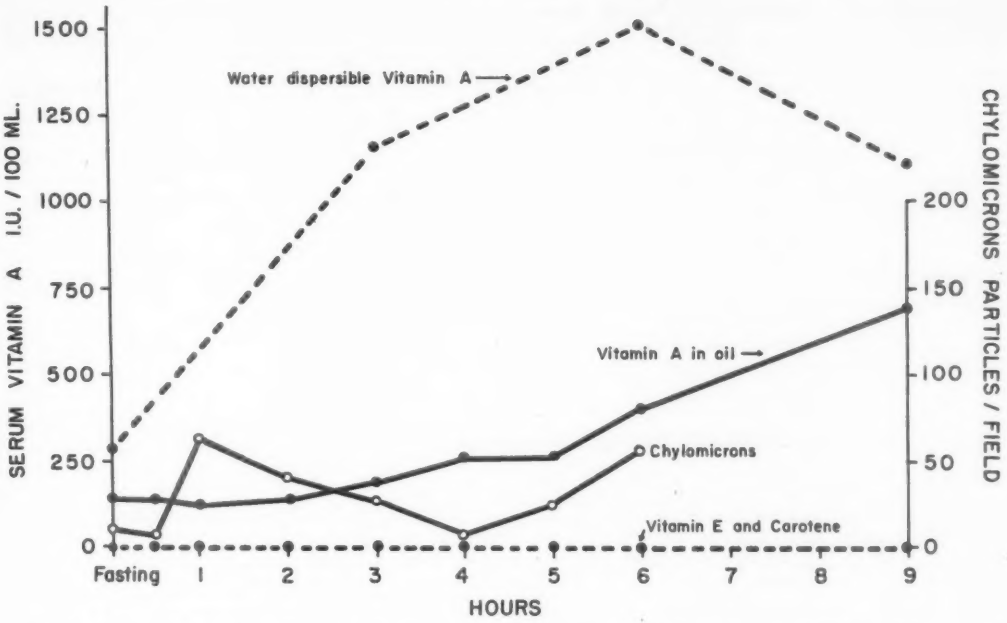

Fig. 1. The serum levels of vitamin A, total tocopherols, carotene and chylomicron counts following a test meal of 650 ml of homogenized milk fortified with 200,000 IU of vitamin A and 600 mg of α-tocopherol. Both carotene and tocopherol levels were 0 in all the determinations. The initial high vitamin A level was due to several days' treatment with a water-dispersible preparation prior to this test. The absorption curve following the administration of 200,000 IU of vitamin A in water-dispersible form (Vi-Penta®-Roche) was performed two days later.

per cent solution in water. Two days later she received 42 ml of the same preparation orally, containing the equivalent of 2.1 grams of α-tocopherol. Massive vitamin D therapy and supplementary calcium were also added to the treatment regimen.

In April, 1954, the patient was readmitted with ascites, pleural effusion, and dependent edema secondary to hypoalbuminemia. The skin xanthomata appeared to be regressing. Bleeding of the gums followed slight trauma. A softening similar to infantile craniotabes was felt on firm pressure over the tibia.

On October 20, 1954, death occurred in another hospital nine days following splenectomy. An autopsy* confirmed the clinical diagnosis of xanthomatous biliary cirrhosis.

* The autopsy was performed by Dr. Chester K. Jones of Jackson, Tenn.

DISCUSSION

As has been predicted,[11] the possible occurrence of signs of vitamin E deficiency in the human might be expected in patients with severe defects in fat absorption who have been treated with a low fat diet for prolonged periods. The present patient had had a significant defect in fat absorption for at least five years prior to the present observations and had been on a low fat diet for over three years. Steatorrhea had been present during most of this period. When first seen, the absence of tocopherols in the blood serum suggested further investigation. In our experience, such extremely low levels of serum tocopherol are rarely found even in patients with sprue.[1] No tocopherol appeared in the serum following a test dose of 600 mg, even when administered with bile salts or when given with the surfactant, Tween 80.

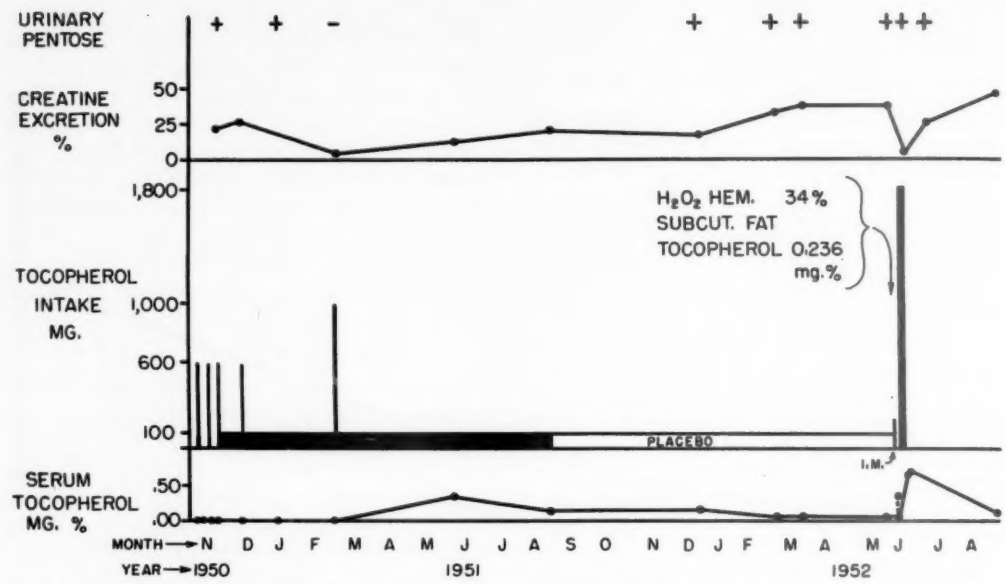

Fig. 2. Serial observations of pentosuria, creatinuria, serum total tocopherol concentrations and doses of tocopherol administered to this patient over a two-year period.

The levels of other fat-soluble vitamins were low and presumably they were poorly absorbed. The initial concentration of vitamin A in the serum was at the lower limits of normal. Although detectable amounts of carotenoids were present in the serum initially, subsequent observation usually failed to detect the presence of carotenoid pigments. The decrease in prothrombin could have resulted from either defective absorption of vitamin K or from liver disease. Because of the severity of the patient's illness, vitamin K therapy was not withheld in order to seek a further fall in prothrombin, but she had observed repeatedly that the bleeding from her gums was controlled by vitamin K administration. Her severe osteomalacia was probably due to reduced calcium absorption. Pathologic fractures ceased to occur following therapy with calcium and vitamin D.

The biochemical findings related to vitamin E nutriture are presented in Figure 2. At the onset, a creatinuria of about 25 per cent of the total creatinine, the presence of a pentose complex in the urine, and the absence of tocopherol in the serum characterized this biochemical picture. After three months of treatment with 100 mg of α-tocopherol daily, in addition to the larger amounts administered for the determination of tocopherol absorption, the creatinuria and pentosuria disappeared. At this time no change in the serum tocopherol followed the administration of 1000 mg of α-tocopherol as an absorption test. After another three months of therapy the serum level had risen to 0.35 mg per 100 ml.

During the nine months following replacement of the tocopherol preparation by a placebo, the pentosuria and creatinuria reappeared and the serum tocopherol level had fallen to 0.05 mg per 100 ml. Hydrogen peroxide hemolysis of red cells (34 per cent) was definitely increased. The muscle biopsy taken at this time showed extreme muscular atrophy without leukocytic infiltration or deposition of ceroid pigment. The biopsy could not be interpreted as characteristic of vitamin E deficiency as seen in the experimental animal. A specimen of subcutaneous fat removed at this time had a tocopherol concentration of 0.236 mg per

100 g.* This is extremely low, usual values for this age group averaging about 9 mg per 100 g.[12]

Because of the difficulty in absorbing fat-soluble preparations of vitamin E, the patient was treated with water-soluble tocopheryl PGS. The intramuscular administration of a single injection of 250 mg of α-tocopherol in this form was not followed by a significant increase in the blood values. Two days later she was given 2.1 g of α-tocopherol in the same form orally. This produced a rise in the serum total tocopherol to 0.33 mg per 100 ml after nine hours, and to 0.62 mg per 100 ml after four days of therapy. This regimen was followed by the disappearance of creatinuria, although the pentose complex continued to be present in the urine. Unfortunately, subsequent determinations of the peroxide hemolysis of the red cells were not considered reliable. Because of extensive pathologic fractures and the bed-ridden state of the patient, it was impossible to make any objective observations concerning muscular strength.

Recent observations by Nitowsky, Gordon, and Tildon[13] in infants with cystic fibrosis of the pancreas and biliary atresia demonstrate a similar correlation of defects in fat absorption with low serum tocopherol concentrations, creatinuria, and decreased resistance to peroxide hemolysis reversible by vitamin E therapy. Their report would suggest that states of poor vitamin E nutriture may occur rather frequently in patients having defective fat absorption. The patients reported by Albright and Stewart[15] and by Cooley and Hartman,[14] for example, have much in common with the present case. This case has been presented with the hope that it will stimulate others to enlarge upon these limited but suggestive observations.

SUMMARY

The association of creatinuria and pentosuria with virtual absence of tocopherols from the blood of a patient with a defect in fat absorption subsisting on a low fat diet for several years has been reported. Increased susceptibility of the red blood cells to hydrogen peroxide hemolysis and an extremely low concentration of tocopherol in the subcutaneous fat were also found. Tocopherol therapy was associated with reduction of creatinuria on two occasions and with disappearance of the pentosuria on one occasion. It is suggested that these biochemical changes represent a deficiency of vitamin E in this patient.

ACKNOWLEDGMENT

The author wishes to thank Dr. William J. Darby for suggesting this investigation and for advice in carrying it out.

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* This analysis was performed by Dr. Dju through the courtesy of Dr. Karl Mason.

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Curiosity, Competition, and Faith

"We seldom stop to think of why we do what we do; in fact, we seldom think philosophically at all. Many a research program is conducted in which the researcher has no clear idea as to just what he is trying to find out or what it would mean if he found it. Men work for years without stopping to examine critically the relevance of their efforts. Curiosity is often the underlying motivation, and not a bad one. It was probably responsible for the discovery by Prometheus of how to make a fire. Emulation is often clearly present, especially when a great scientist is surrounded by disciples. The competitive spirit, fortunately now on a more friendly basis than in the past, has a strong part in scientific motivation. It has become less artificial and less acrimonious as caste distinctions and false pride have lost their hold and as the stuffed shirts among us have dwindled almost to extinction. And the sporting instinct, whatever that is, which causes men to pit themselves against great odds, to revel in trial and adversity, to breathe the stimulating air of self justification in success, no doubt is often present. We do what we do for many unavowed reasons, and seldom pause to analyze them. But when we do reflect, we find that our primary motivations in scientific effort extend far beyond our casual and momentary reasons, even beyond the thought that what we do may, in its small way, benefit the human race in its struggle to control its environment and itself in the grim days that are sure to come.

For the scientist lives by faith quite as much as the man of deep religious convictions. He operates on faith because he can operate in no other way. His dependence on the principle of causality is an act of aith in a principle unproved and unprovable. Yet he builds on it all his reasoning in regard to nature."
—Vannevar Bush. *Report of the President of the Carnegie Institution of Washington*, December 9, 1955, p. 6.

Hypervitaminosis A

EXPERIMENTAL INDUCTION IN THE HUMAN SUBJECT

By ROBERT W. HILLMAN, M.D.*

With the technical assistance of MARIE E. LEOGRANDE

VITAMIN A toxicity is a well-documented phenomenon. Experimentally, pathological changes are readily reproduced in animals fed an excess of this nutrient[1–6]. Clinically, a characteristic syndrome of chronic poisoning is emerging from reports of patients consuming concentrated preparations of vitamin A over long periods of time.[7–16] Children, particularly, have been afflicted, but at least five instances have been recorded in adults. Gerber, Raab, and Sobel[17] published the most comprehensive of these descriptions and reviewed the literature on the subject. The biochemistry and pathology of hypervitaminosis A have recently been discussed by Nieman and Klein Obbink.[18]

The present report describes the experimental production of hypervitaminosis A in man. The attempt was made to demonstrate relationships between the quantity of vitamin ingested, its concentration in the blood plasma, and clinical and laboratory evidence of a "toxic" reaction to this substance. Repetition of the procedure in the same subject tested the reproducibility of the results and provided some indication of intra-individual variation in response to comparable dosage during two separate periods of administration (Table I).

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METHOD

The subject was a 40-year-old white male physician of moderately athletic habitus, 71 inches in height and weighing 165 pounds. He was in generally good health, although there was a past history of malaria, hepatitis, and dysentery. Prior to, and between—but not during—the two experimental periods five months apart, there was irregular consumption of a multivitamin preparation containing 5000 International Units of vitamin A. In the four-month period ending one month prior to the beginning of the first experimental period, there was additional consumption (by mouth, chiefly, and intravenously) of approximately 2.5 million International Units during a series of vitamin A tolerance tests. Over a period of more than one-half year fasting blood levels had been fairly constant, falling within the range of accepted normal values. No attempt was made to standardize or in any way modify living habits or dietary intake during these tests.

The vitamin A preparation employed was an aqueous emulsion (Aquasol), which has been shown to be better absorbed than the oil preparations incriminated in most reported instances of hypervitaminosis. Although the toxic dose of vitamin A has been variously estimated,[18] it would be expected to prove relatively smaller with this water-miscible product.[19–21]

In the first experimental period, during the month of December, one million units of vitamin A were ingested daily for 13 days, in inconstant portions and at irregular hours between 8:00 a.m. and 10 p.m. Two million units were

ingested within one-half hour on the fourteenth and final day.

Vitamin A adsorption tests were performed on the ninth, eleventh and fourteenth day. In each of these tests, the blood vitamin A level was measured in the postabsorptive state and at intervals of one and four hours after the test dose. One million units were administered in the first two tests, and two million units in the third. The subject fasted throughout the first and last tests, but consumed a small breakfast at the one-hour point in the second—to evaluate the possible effect of eating on absorption of this type of vitamin A preparation.[22]

The second experimental period was in the following May, a time selected to present possible contrasting seasonal influences and to permit a long interval of apparent clinical normality. One million units of the same preparation were ingested daily for a period of 25 days. The effects of ethanol on the plasma vitamin A level were measured in the postabsorptive state on the fifth and thirteenth days of this period. In the first of these, 60 ml of 100 per cent ethyl alcohol (diluted with 200 ml of carbonated water) were taken by mouth, and, in the second, one liter of a 5 per cent solution was administered intravenously over a period of 20 minutes. Blood plasma vitamin A levels were measured before, and at intervals of 1, 2, and 4 hours after the start of each test.

With the exceptions noted in the absorption and ethanol tests, all blood specimens were drawn in the fasting state during control, interval and experimental periods. The plasma vitamin A preparation was measured in duplicate by the ultraviolet irradiation method of Bessey *et al.*,[23] adapted to 3-ml samples.

In the second experimental period the following additional tests were performed: sedimentation rate, serum bilirubin, cholesterol concentration, cephalin flocculation and thymol turbidity, the last four to evaluate possible adverse effects on the liver—the principal storage site of vitamin A. On the final day of this period, roentgenograms were made of the pelvis and of the long bones of the extremities, which are among the principal sites of abnormalities reported in cases of hypervitaminosis A.[5,10,12,17,18]

Dark-adaptation studies were performed on three separate occasions, one before and two during the second experimental period—on the hypothesis that, since some lesions associated with vitamin A excess resemble those resulting from a deficiency of this substance[14] and of other nutrients,[15] a similar effect might be manifested in retinal function.[24–26]

RESULTS

Results are indicated in the accompanying tables and figure.

The responses during the two experimental periods differed considerably—both qualitatively and quantitatively. This was especially true with respect to the clinical manifestations of vitamin A toxicity. In the first period the degree of debility was sufficient to cause vitamin A consumption to be discontinued at the end of two weeks. In the second, the symptoms were most pronounced from the third to the tenth day, following which discomfort and functional inefficiency declined, to remain fairly constant for the remainder of the experiment. However, the subjective "recovery period" was longer following the second test period, about four, compared with two, weeks.

The principal clinical features included the following: headache (severe, often intractable, chiefly frontal and retro-orbital): pruritic dermatitis, including folliculosis and xerosis, notably of the extremities, generalized desquamation, exacerbation of pre-existing seborrhea (principally of the scalp), and an apparent increment in a long-developing alopecia; increased fragility of the fingernails;* cheilosis, with marked chapping and splitting of the lips; epistaxis, slight but persistently induced by blowing the nose; gastrointestinal disturbances, including anorexia, nausea, and alternating constipation and diarrhea with severe

* The increased fragility was noted some three months after each test period, at a time when the segments of nails formed under these abnormal conditions reached the distal margins. There was no significant difference in the measured rate of nail growth between the experimental and control periods.

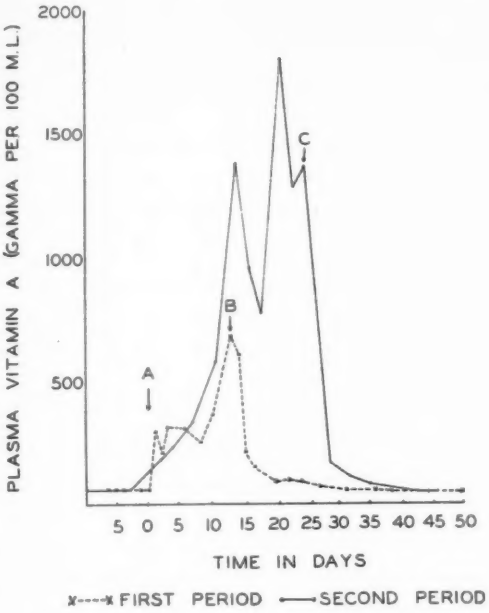

Fig. 1. Blood plasma vitamin A levels during two test periods of ingestion (one million units daily*). *A*, Vitamin A started, both test periods. *B*, Vitamin A discontinued, first test period. *C*, Vitamin A discontinued, second test period.

* Two million units on final day, first period only.

TABLE I

Blood Plasma Vitamin A Concentrations Associated with Ingestion of Excessive Doses

First Period			Second Period		
Date	*Test day	†Vit. A	Date	Test day	Vit. A
12/2	−5	50	4/8	−26	54
12/3	−4	54	4/22	−12	45
12/6	−1	57	4/29	−5	48
12/7	1	62	5/4	3	174
12/8	2	288	5/6	5	232
12/9	3	192	5/9	8	321
12/10	4	298	5/13	12	574
12/13	7	286	5/16	15	1391
12/15	9	247	5/18	17	961
12/17	11	359	5/20	19	784
12/20	14	686	5/23	22	1803
12/21	+1	612	5/25	24	1286
12/22	+2	206	5/27	+1	1368
12/23	+3	144	5/31	+5	156
12/26	+6	98	6/3	+8	125
12/27	+7	79	6/6	+11	84
12/29	+9	85	6/13	+18	64
12/31	+11	78	6/15	+20	60
1/3	+14	67	6/17	+22	61
1/7	+18	52	6/22	+27	66
1/12	+23	58	7/6	+41	45
1/14	+25	53	7/12	+49	59

Mean plasma vitamin A concentration

(a) Before first test period (40 readings from 5/18–11/30/54) 59.5 ± 7.8 with a range of 44–75 μg per 100 ml.

(b) Between test periods (9 readings from 1/24–4/1/55) 47.1 ±6.6 with a range of 42–56 μg per 100 ml.

(c) Following second test period (8 readings from 7/15–9/8/55) 48.4 ± 6.7 with a range of 34–46 μg per 100 ml.

* Days before, during, and following ingestion period.

† Vitamin A concentration in micrograms per 100 ml of plasma.

tenesmus; visual disturbances, including seeming diminished acuity and development of spots before the eyes (one of which has persisted during the seven months since the end of the second test period); transient dizziness; generalized muscle weakness and fatigability; polyarthralgia; and pain and tenderness over the long bones, notably the distal tibia.

These manifestations did not all appear during each experimental period, nor did they necessarily become more severe or remain constant once they became evident. The epistaxis was noted only in the first, shorter period, during which, too, the dermatitis was much more severe and widespread. A generalized desquamation, lasting approximately two weeks, began only after the first course of vitamin A was discontinued. During the second, a much less pronounced desquamation began on the fourteenth day (comparable to the first-period fortnight), continued throughout the remaining days of vitamin ingestion, and persisted for three weeks after it was discontinued.

Most striking and variable among the clinical manifestations were the headache and cheilosis. The former was severe throughout the first period and even more severe during the first week of the second trial, but became mild and inconstant thereafter.

The cheilosis, present continuously after the first few days of both periods, became in-

TABLE II

Blood Plasma Vitamin A Levels During Vitamin A Absorption Tests and in Response to Oral and Intravenous Ethyl Alcohol

Test no.	Date	Test period	Test period day	Test substance and experimental conditions	Plasma vit. A level*			
						Time in hours†		
					Fasting	1	2	4
1	12/15	1	9	Aqueous vitamin A, 1 million units, fasting throughout	247			1001
2	12/17	1	11	Aqueous vitamin A, 1 million units, small meal 1 hour after test dose	359	367		1224
3	12/20	1	14	Aqueous vitamin A, 2 million units, fasting throughout	686	716		3094
4	5/6	2	5	Ethanol, 100%, 60 ml and 200 ml water by mouth, fasting throughout	232	232	268	240
5	5/13	2	12	Ethanol 5%, 1 liter intravenously, fasting throughout†	574	410	424	538

* Vitamin A level in micrograms per 100 ml.

† Time after ingestion of test substance, and from beginning of alcohol infusion (infusion time 20 minutes).

creasingly severe throughout the second period, to disappear finally about two weeks later.

The blood vitamin A patterns were comparable during the two test periods (Fig. 1). Although the first pattern was smoother, both showed an irregular, but generally progressive, rise in plasma concentration, followed by a rapid fall when the vitamin was withheld. However, the relative plateau level of 200 to 300 micrograms per 100 ml during approximately the first half of the first period had no real counterpart in the later trial, and, beyond the initial drop, the falling plasma level also seemed more gradual in the earlier test. Vitamin A was not detected in the urine when the plasma concentration was elevated.

The patterns of the vitamin A absorption tests and the plasma level responses to ethanol are indicated in Table II. In each of the absorption tests, the blood concentration increased by well over 200 per cent (over 300 per cent in two instances). The response did not seem significantly enhanced by the ingestion of food one hour after the administration of the vitamin.

Ethanol by mouth increased the plasma vitamin A level by approximately 15 per cent, but there was no apparent increase following the ethanol infusion. Correction was not made for the dilution factor (1 liter introduced into the blood stream), although similar infusions have been followed by a rise in plasma vitamin A concentration from normal levels in the same subject.

In general, although there was a good correlation between the amount of vitamin A ingested and the resultant blood levels, a corresponding correlation between the blood levels and the clinical manifestations was not observed. The more prolonged convalescence following the second, longer consumption period was, however, more consistent with expectations.

The serum cholesterol, bilirubin, cephalin flocculation, and thymol turbidity tests showed no significant changes during the experimental period in which these were performed. The blood sedimentation rate fluctuated from normal to slightly elevated readings, but there was no apparent correlation between this rate and the plasma vitamin A level. Dark-adaptation measurements did not vary significantly during the test period, and ophthalmologic examination at the conclusion of the experiment revealed no unusual findings.

DISCUSSION

The manifestations of vitamin A toxicity observed in this experimental production of the syndrome are similar to those reported in cases of accidental poisoning with this substance. The principal features of the present

study are (1) the apparently poor correlation between the blood plasma levels and the clinical reaction to excess vitamin A, and (2) the different responses in the same subject at different times.

The probable influence of factors other than the amount of vitamin consumed must, of course, be considered.[19,27,28,29] Mild, unnoted, intercurrent infections could conceivably have contributed to the symptoms and influenced plasma vitamin A concentrations. Emotional reactions, engendered by concern over toxic manifestations, undoubtedly modified subjective observations, at least. The more pronounced skin reactions noted during the first test period may have resulted in part from the colder weather that commonly conduces to the development of follicular and xerotic lesions in particular.

The generally less severe clinical picture during the second experimental period suggests that observed variations were not related to an excess of vitamin A retained (in the liver) over the interval of five months.[18]

Hypervitaminosis A, representing an abnormal concentration of this substance in the blood plasma, and, presumably, in other tissues, is apparently not synonymous with clinical toxicity referable to an excessive intake of this substance. Comparable to the experience of Arctic explorers, whose acute illness shortly following the ingestion of polar bear liver has been attributed to the large concentrations of vitamin A in this organ, i.e., to acute poisoning,[30] the evidence suggests that symptoms reflect, at least in part, a relative individual hypersusceptibility. As in the case of vitamin D—with which it has much in common—untoward reactions to this fat-soluble vitamin probably occur in only a small number of individuals consuming excessive quantities. Moreover, there seem to be states of relative refractoriness to vitamin A therapy, analogous to vitamin D-resistant rickets. These instances, like relative resistance to clinical toxicity, may possibly be eliminated by the use of better absorbed, aqueous preparations, such as the one used in this experiment.[19–21]

Depending on the criteria used, this case could be regarded as an example of either acute or chronic vitamin A toxicity.[13] Moreover, since many of the symptoms and signs, particularly in the skin, are evidently observed in both types of poisoning, the clinical distinction between acute and chronic syndromes appears artificial and necessarily arbitrary in some instances. Beyond a limited capacity for storage, destruction, or other effective metabolic neutralization (but evidently not excretion) of vitamin A,[18] toxicity caused by this substance would seem to relate to a pharmacologic constant—the product of dose and duration—in which the factor of intensity can be substituted to some degree for that of time, in bringing about a given physical effect. As suggested by the symptom pattern during the second experimental period, the response to absorption tests, and by other reports of clinical toxicity,[16] some adaptation to hypervitaminosis A evidently can occur, with a concomitant modification of the clinical picture. Comparable periodicity of symptoms with temporary spontaneous remissions has been noted in experimental animals.[18] In man, too, apparent compensation for high vitamin intakes, through mechanisms which regulate plasma concentrations, has been described.[27]

The results of the present study confirm the protean manifestations of vitamin A toxicity and the particular predilection for the skin and its derivatives, the hair and nails. More significantly, they establish the existence of intra-individual variation in response to excessive doses of this substance and suggest that the imponderable factor of the human host determines to a very considerable degree the clinical picture (if any) associated with hypervitaminosis A.

SUMMARY

Hypervitaminosis A was induced experimentally in a normal human subject on two separate occasions through ingestion of excessive quantities of this substance during periods of 14 and 25 days, respectively.

The associated clinical picture resembled that of accidental vitamin A poisoning. The skin was most prominently affected. The plasma vitamin A concentration increased

markedly, and appeared to be more closely correlated than the clinical picture with the quantity of vitamin A ingested.

Differences in the responses to comparable doses during the two test periods seemed to reflect principally a considerable intra-individual variation in susceptibility to poisoning with this nutrient.

ACKNOWLEDGMENTS

Appreciation is expressed to Dr. Philip Cabaud for the liver function tests, to Dr. John Wentworth for the roentgenographic studies, to Dr. Harold Schilback for the ophthalmological examination, and to Dr. Charles Haig of New York Medical College for the dark-adaptation studies.

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Absorption of Iron from the Gastrointestinal Tract

A COMPARATIVE STUDY OF THE ORAL IRON TOLERANCE TEST IN HUMAN BEINGS USING STABLE AND RADIOACTIVE IRON

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With the technical assistance of DIANA STEINHOUSE

THE SIGNIFICANCE of changes in serum iron levels after the ingestion of large doses of stable iron has been questioned as a valid index of iron absorption.[1,2,3,4] It is apparent that not only the rate of absorption, but also the rate of removal of iron from the blood determines the serum levels.

Previous work in this laboratory has utilized an oral iron tolerance test with stable iron in an endeavor to study iron absorption in states of health and disease.[5] This study was undertaken in an attempt to evaluate the accuracy of the Ramsey method[6] for the determination of serum iron by comparing the recovery of stable iron in the serum after oral administration with the recovery of simultaneously administered radioactive iron in the serum. Furthermore, it was desired to ascertain whether or not these values for serum recovery bear any relationship to the total absorption of Fe^{59} as determined both by stool analysis and recovery of Fe^{59} in the hemoglobin.

METHODS

An iron tolerance test was performed. In most instances stable iron was given in the form of ferrous ammonium sulfate and radioactive iron as ferric chloride (Fe^{59}). In normal subjects the absorption of ferric stable and ferric radioactive iron was studied with and without the addition of ascorbic acid. In a small series ferrous stable and ferrous radioactive iron (Fe^{59}, as ferrous gluconate) were given for comparison with the other groups. Stable iron in the amount of 1 mg per kilogram of body weight and radioactive iron in tracer doses of the order of 10 to 15 microcuries (0.001–0.016 mg elemental iron per microcurie) were given orally. The radioactive iron was purchased from the Abbott Laboratories.

All subjects were given the iron (both stable and radioactive) by mouth, after a fast of 10 to 16 hours. They were allowed no food until after the completion of the test. Specimens of venous blood were drawn immediately preceding the test and hourly thereafter for four hours. Serum iron levels were determined by the Ramsey method.[6] Values of 100–170 μg per 100 ml were considered normal fasting levels in our laboratory. Latent iron-binding capacity was determined by the method of Rath and Finch,[7] using a Klett colorimeter (Model #800-3). Estimations of per cent recovery of stable iron in the serum were calculated from the difference at each hour between the serum iron and the fasting serum iron, multiplied by the plasma volume, and divided by the total dose of stable

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This work was supported in part by the Research and Development Division, Office of the Surgeon General, Department of the Army, Contract No. DA-49-007-MD-524. Supported in part by a grant from the Commonwealth Fund.

iron. Plasma volume was estimated by means of the hematocrit and an assumed blood volume of 84 ml per kilogram in males, and 78 in females.[8,9]

Radioactivity in the samples was measured in the following ways. Standard for the test dose was a 2-ml aliquot taken from a 100-ml volumetric flask containing the test dose of ferric or ferrous radioactive iron as the chloride or the gluconate. This aliquot was immediately made up to 100 ml with water acidified with concentrated sulfuric acid to a pH between 1 and 2. This was necessary to prevent precipitation of iron and its consequent adherence to the glassware. Five-ml aliquots of the acidified solution were counted for radioactivity in a gamma-ray scintillation well-type counter (Nuclear-Chicago Model #DS 3). Counting of radioactivity was performed to greater than 2 per cent statistical accuracy on samples of over 1000 counts per minute and to at least 5 per cent statistical accuracy on samples of less than 1000 counts per minute. Background averaged 128 counts per minute.

Specimens of 5 ml of serum were pipetted into iron-free tubes and measured for radioactivity prior to chemical analysis. Measurements of stable iron were subsequently carried out on these same aliquots of sera. Blood was taken into a bottle containing dry potassium oxalate, a 5-ml sample was pipetted immediately into a measuring tube, and, after hemolysis had occurred by freezing and thawing, it was read for radioactivity. In estimating the activity of the blood, the blood volume assumption was as above. Blood was drawn three times weekly in the second and third weeks after the tracer dose was given in early subjects (Table IIa, b, c), and after one to two months in later ones (Tables Ia, b, c, and IId, e).

The feces passed each day were collected and weighed. Each specimen was homogenized in an electric blendor and transferred in 5-ml aliquots to a weighed tube for counting. The weight of each 5-ml aliquot was determined, and total recovery of radioactivity estimated on this basis. Fecal collections were continued until the activity of the stools on two successive days measured less than 1 per cent of the administered dose. Later stool collections were limited to seven days; as in most earlier subjects all appreciable radioactivity was excreted in this interval.

Iron absorption studies were performed on 34 subjects. Twelve subjects were considered as normal controls; one of these was recovering from a spontaneous pneumothorax. Five subjects convalescent from coronary occlusion (three weeks post coronary occlusion) and one subject with axillary vein thrombosis and pulmonary infarction, all of whom appeared hematologically normal, were originally selected as controls, but this group will be considered separately as their absorption data differed somewhat from those of the healthy controls. Seventeen other patients with a wide variety of diseases were studied by the iron tolerance test.

RESULTS AND INTERPRETATION

In the healthy group several combinations of iron salts (in reduced and unreduced states, with and without ascorbic acid as a reducing agent) were administered. Three subjects received both ferric stable and ferric radioactive iron without ascorbic acid (Table Ia); in this group only meager absorption of iron was demonstrated, either in serum or hemoglobin (in fact radioactivity was too low for satisfactory counting to statistical accuracy), and recovery of administered Fe_{59} in the feces was maximal. A comparable group of controls (Table Ib) who received the same combination of iron salts plus 500 mg of ascorbic acid administered simultaneously showed excellent iron absorption, even at one hour, and the recovery of Fe_{59} in the stools was proportionately low (Fig. 1). Comparably good results were obtained in two control subjects receiving both stable and radioactive ferrous iron (Table Ic). Four normal controls were given stable ferrous iron and radioactive ferric iron (Table Id); in this group recovery of stable iron in the serum was as large as that of the reduced ferric (Table Ib) and the ferrous series (Table Ic) (Fig. 2). However, recovery of radioactive iron in serum was consistently less than that of stable iron, and recovery of radioactive iron in hemoglobin and its estimated absorption by the stool technique

were somewhat less than in the other control groups (Table Ib, c) in which the tracer was given in the reduced state. It has been shown that a large quantity of ferrous iron is capable of reducing ferric iron,[10] and the demonstrable absorption of the isotope in the series shown in Table Id confirms this phenomenon. However, the tendency to a smaller recovery of Fe^{59} than of stable iron in the serum samples suggests that the reduction of the iron to the ferrous state was only partial, at least during the four-hour period devoted to serum collection.

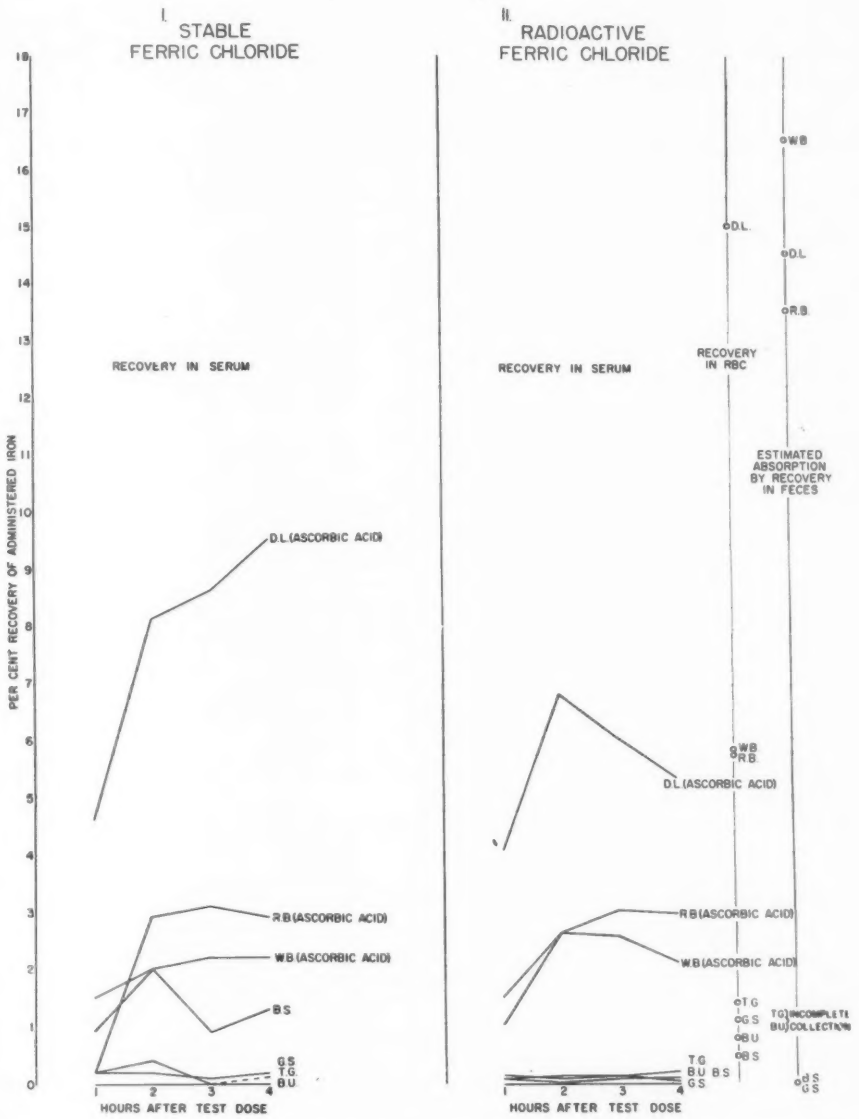

Fig. 1. Response of normal subjects to ferric stable and radioactive iron, with and without simultaneously administered ascorbic acid.

TABLE I. Normal Subjects

Subject	Age	Sex	Wgt.	Hct.	Latent iron-binding capacity	Fasting serum Fe		% Recovery of iron, hours 1	2	3	4	Maximum rise serum Fe	% Recovery of Fe^{59} Stool	Blood	Serum	Diagnosis
						μg/100 ml						μg/100 ml				
a. Ferric Stable, Ferric Fe^{59}																
B. U.	31	M	56	48	250	125	Isotope	0.12	0.07	0.10	0.11	2	89.0*	0.8	0.1	Normal
							Stable	0.9	2.0	0.9	1.3					
B. S.	27	M	78.4	48	200	110	Isotope	0.17	0.12	0.14	0.08	45	113.0	0.5	0.2	Normal
							Stable	0.9	2.0	0.9	1.3					
T. G.	24	M	68	48	200	200†	Isotope	0.11	0.15	0.14	0.21	10	98.8	1.4	0.2	Normal
							Stable	0.2	0.4	0	—					
b. Ferric Stable, Ferric Fe^{59} + Ascorbic Acid																
D. L.	27	M	77	48	225	165	Isotope	4.0	6.8	6.0	5.3	115	85.0	15.1	6.8	Normal
							Stable	4.6	8.1	8.6	9.0					
R. B.	27	M	73	42	—	160	Isotope	1.1	2.6	3.0	3.0	70	86.0	5.7	3.0	Normal
							Stable	0.2	2.9	3.1	2.9					
W. B.	25	M	63.6	43	200	165	Isotope	1.5	2.6	2.6	2.1	50	83.0	9.6	2.6	Normal
							Stable	1.5	2.0	2.2	2.2					
c. Ferrous Stable, Ferrous Fe^{59}																
P. K.	19	M	57	49	200	125	Isotope	2.5	3.1	2.9	2.4	95	88.9	9.9	3.1	Spontaneous pneumothorax (no anemia)
							Stable	2.0	3.5	4.6	4.6					
M. D.	20	M	75	46	250	140	Isotope	3.1	3.3	2.8	2.0	90	95	13.3	3.1	Normal
							Stable	3.1	3.3	3.5	4.0					
d. Ferrous Stable, Ferric Fe^{59}																
E. H.	30	M	66	46	200	160	Isotope	3.0	3.2	2.4	0.3	135	91	8.0	3.2	Normal
							Stable	3.5	5.9	4.4	—					

TABLE I. Normal Subjects—*cont'd.*

Subject	Age	Sex	Wgt.	Hct.	Latent iron binding capacity	Fasting serum Fe		% Recovery of iron, hours				Maximum rise serum Fe	% Recovery of Fe^{59}			Diagnosis
								1	2	3	4		Stool	Blood	Serum	
					μg/100 ml							*μg/100 ml*				
							d. Ferrous Stable, Ferric Fe^{59}									
B. H.	34	M	89	42	250	140	Isotope	2.3	3.0	2.7	0.9	180	92	6.3	3.0	Normal
							Stable	2.2	7.9	5.7	—					
D. B.	32	M	80	45	—	130	Isotope	0.2	0.4	0.2	0.2	140	94	4.0	1.2	Normal
							Stable	1.3	2.2	2.2	—					
H. E.	26	M	66	45	—	160	Isotope	0.8	1.4	1.1	0.5	130	95	2.4	1.4	Normal
							Stable	1.7	5.7	4.6	4.0		Mean 7.0% absorption	Mean 5.2%		

* Incomplete collection.

† Slightly higher than our usual "normal" range; unexplained.

In summary, normal subjects showed a prompt rise in serum iron concentration after the ingestion of ferrous stable iron, followed by the appearance of radioactive iron in the hemoglobin with a mean of 5.2 per cent (Table Id) if the isotopic iron was administered in its ferric form simultaneously with a large quantity of ferrous stable iron; and the total absorption based on stool analysis gave a mean value of 7 per cent (Table Id). Better absorption of isotopic iron was demonstrated when the tracer was either given in the reduced form or was reduced simultaneously with stable iron by a large dose of ascorbic acid.

The iron tolerance test using ferrous stable iron and ferric radioactive iron was employed in the majority of patients studied, as the ferrous isotope was not available to us until later in the study. Though there were several exceptions, the tendency to greater recovery of stable iron than of radioactive iron in the serum occurred in the patients as well as in the normal subjects, and can probably be explained by incomplete reduction of the radioactive iron. The absorption of iron in these patients varied from greater than the controls in subjects with evidence of iron deficiency (Table IIa)(Fig. 2), to very poor absorption in several patients (Table IIb). The bulk of the patients appeared to absorb iron as well as the controls (Table IIc); in several of this group normal hematocrits were observed, but a depression of the fasting serum iron and a slight elevation of the latent iron-binding capacity (L.I.B.C.) suggested iron deficiency[7] (S. C., M. S., J. Su.), and in these the degree of absorption was only slightly greater than or the same as for the rest of the group. This was not a constant observation, however, as one patient (R. B.) with higher than normal latent iron-binding capacity and lower than normal fasting serum iron demonstrated evidence of slightly less absorption.

No definite correlation of the type of disease process and the degree of iron absorption can be made from this small series, and hence no statistical analysis has been attempted. Several specific cases are worthy of mention, how-

TABLE II. Patients

Subject	Age	Sex	Wgt.	Hct.	Latent iron-binding capacity	Fasting serum Fe		% Recovery of iron, hours 1	2	3	4	Maximum rise serum Fe	% Recovery of Fe^{59} Stool	Blood	Serum	Diagnosis
						μg/100 ml						μg/100 ml				
							a. Ferrous Stable, Ferric Fe^{59}									
N. H.	63	F	50	32	325	52	Isotope	8.2	7.2	6.1	5.1	173	76	—	8.2	Pancreatitis CVA ASHD, (hypochromic anemia)
							Stable	3.7	6.1	9.3	8.0					
S. W.	81	F	55	40	400	80	Isotope	10.2	11.5	10.3	8.7	370	70	26.8	11.5	Carcinoma of esophagus (hypochromic anemia)
							Stable	7.0	15.9	17.1	17.3					
T. C.	50	F	57	30	400	45	Isotope	7.4	5.8	4.6	3.7	195	78	24.5	7.3	Lupus erythematosis (hypochromic anemia 2° to menstrual blood loss)
							Stable	6.3	10.7	10.1	8.5					
							b. Ferrous Stable, Ferric Fe^{59}									
F. O.	51	F	84	35	100	105	Isotope	0.8	0.4	0.2	<0.1	100	98	—	0.8	Myelogenous leukemia (chronic) (transfusions)
							Stable	1.5	0.8	0.0	0.0					
A. G.	53	F	36	39	150	150	Isotope	0.6	0.6	0.5	0.5	70	98	1.7	0.6	Sprue syndrome
							Stable	5.7	5.7	5.7	2.4					
F. H.	58	M	55	50	100	240	Isotope	0.4	0.3	0.4	0.4	0	98	2.2	0.4	Hemochromatosis (biopsy of liver)
							Stable	0.0	0.0	0.0	0.0					
P. P.	49	M	88	50	200	220	Isotope	0.6	0.9	0.9	1.0	25	98	—	1.1	Diabetes, cirrhosis, gangrene (no hemachromatosis)
							Stable	0.8	1.1	0.8	0.6					
J. F.	29	F	58	38	225	65	Isotope	0.5	0.5	0.3	0.1	95	*	—	0.5	Hypochromic, mycrocytic anemia (?thalassemia minor)
							Stable	3.1	3.1	0.7	0.2					
							c. Ferrous Stable, Ferric Fe^{59}									
M. O.	55	F	40	30	150	80	Isotope	3.1	3.1	2.8	2.0	110	*	—	1.3	Chronic nephritis, uremia
							Stable	6.6	6.0	6.0	6.0					
M. C.	72	F	54	40	150	70	Isotope	2.4	2.3	2.0	1.3	92	95	—	2.4	Laennec's cirrhosis (compensated)
							Stable	3.3	4.2	4.4	3.7					
																Agnogenic

Subject	Age	Sex	Wgt.	Hct.	Latent iron-binding capacity	Fasting serum Fe		% Recovery of iron, hours 1	2	3	4	Maximum rise serum Fe	% Recovery of Fe^{59} Stool	Blood	Serum	Diagnosis
						μg/100 ml						μg/100 ml				
M. C.	72	F	54	40	150	70	Isotope	3.3	4.2	4.4	3.7	92	95	—	2.4	Laennec's cirrhosis (compensated)
							Stable									
																Agnogenic myeloid

Subject	Age	Sex	Wgt.	Hct.	Latent iron-binding capacity	Fasting serum Fe		% Recovery of iron, hours 1	2	3	4	Maximum rise serum Fe	% Recovery of Fe^{59} Stool	Blood	Serum	Diagnosis
						μg/100 ml						μg/100 ml				
H. F.	45	F	57	30	150	150	Isotope	3.9	2.0	2.2	4.3	70	88.5	12.2	3.9	Lupus erythematosis, and septicemia
							Stable	2.2	3.8	3.8	1.6					
S. C.	27	F	53	41	225	90	Isotope	2.5	3.0	3.7	2.0	130	89	12.0	3.7	Infectious mononucleosis, myocarditis
							Stable	3.2	8.2	8.2	7.6					
M. S.	51	F	77	36	375	45	Isotope	5.2	5.0	4.7	3.9	150	*	—	5.2	Diabetes, femoral thrombophlebitis
							Stable	3.2	7.2	8.0	7.7					
A. B.	67	F	78	36	—	120	Isotope	2.7	3.5	3.2	2.3	175	*	—	3.5	Muscular dystrophy
							Stable	3.5	8.7	8.7	7.5					
J. Su.	63	M	88	32	350	110	Isotope	0.4	0.7	0.5	0.3	130	90	8.6	3.4	Hypochromic anemia—?, 2° to peptic ulcer
							Stable	1.1	6.3	6.3	6.3					
R. B.	53	M	50	39	325	40	Isotope	1.0	2.5	3.0	3.0	110	92	—	2.6	Rheumatic heart disease, chronic CHF
							Stable	4.1	5.6	5.4	5.1					
							d. Ferrous Stable, Ferric Fe^{59}									
J. P.	47	M	85	46	—	180	Isotope	1.5	1.7	1.3	0.7	90	96	3.5	1.7	Coronary occlusion (no anemia)
							Stable	2.7	4.1	3.9	0.5					
J. W.	41	M	61	43	150	180	Isotope	0.3	0.3	0.2	0.1	40	99	0.6	0.3	Axillary vein thrombosis, pulmonary infarction (no anemia)
							Stable	1.9	1.9	1.7	0.0					
							e. Ferrous Stable, Ferrous Fe^{59}									
C. T.	64	M	55.6	47	200	135	Isotope	1.0	1.3	1.1	1.9	40	87.3*	—	1.3	Coronary occlusion (3 weeks), ASHD (no anemia)
							Stable	1.8	1.8	1.3	1.1					
J. A.	50	M	79.6	49	200	80	Isotope	0.5	0.5	0.4	0.3	40	94.4	—	0.5	Coronary occlusion (3 weeks) (no anemia)
							Stable	0.7	0.4	1.5	1.8					
J. M.	44	M	61.6	45	—	75	Isotope	0.6	1.2	1.1	0.8	30	—	9.2	1.2	Coronary occlusion (4 weeks) (no anemia)
							Stable	0.0	0.9	1.3	0.9					

* Incomplete collection. CVA—cerebrovascular accident. ASHD—arteriosclerotic heart disease. 2°—secondary to. CHF—congestive heart failure.

ever. One patient (F. H.) with hemochromatosis (proved on biopsy) appeared to absorb less iron than the controls; this is not consistent with recent reports in the literature.[11,12] One patient (J. Su.) with hypochromic anemia and evidence of iron deficiency by fasting serum iron level and latent iron-binding capacity appears to have had delayed absorption, as the serum recoveries are low, but the stool and hemoglobin recoveries are consistent with the other iron-deficient patients. This discrepancy may have been due to delayed gastric emptying, as this patient had a peptic ulcer and may have had some degree of duodenal obstruction,

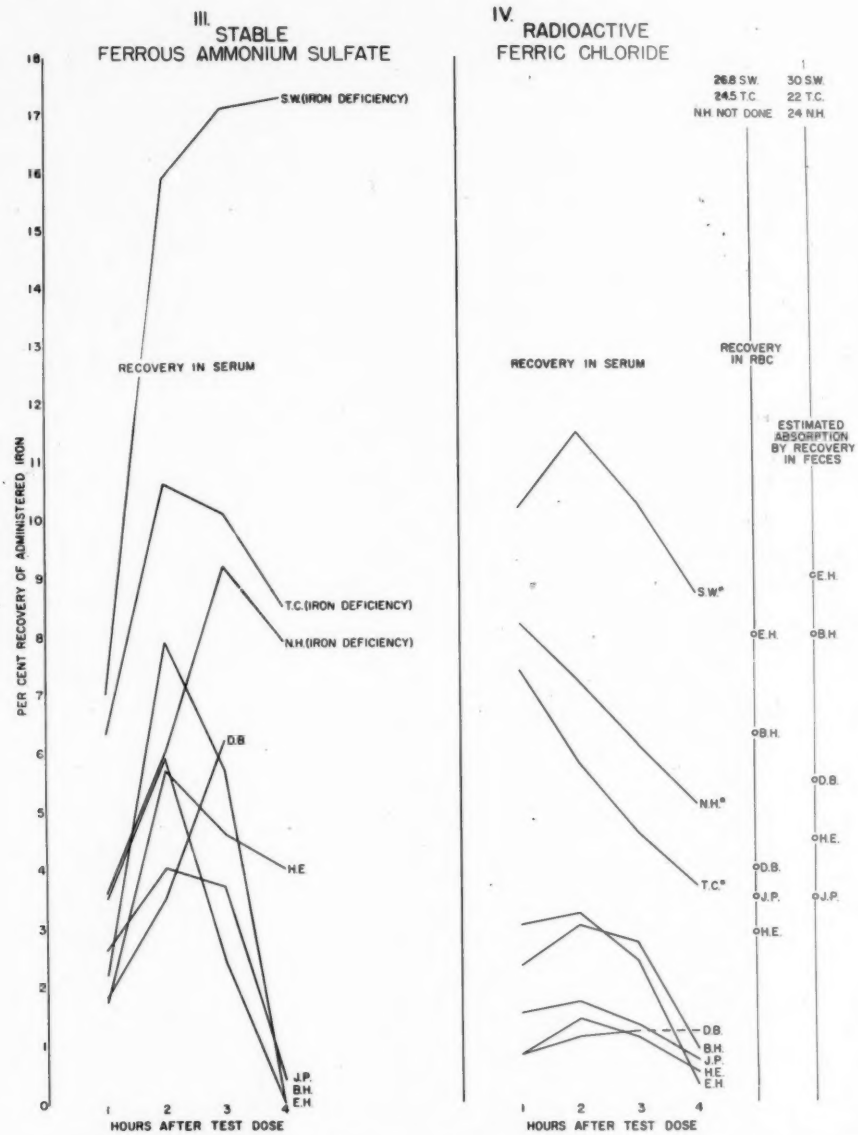

Fig. 2. Response of normal subjects to simultaneously administered stable ferrous iron and radioactive ferric iron.

although there was no definite clinical evidence of this. An interesting finding in the group of patients with coronary occlusion and the one patient with axillary vein thrombosis and pulmonary infarction (Table IId, e), originally selected as controls, was evidence of generally poor iron absorption, consistently in the serum recoveries and frequently in the hemoglobin recovery of Fe_{59} or by the stool analysis, although two patients (J. P. and A. M.) showed normal hemoglobin recovery.

DISCUSSION

In evaluating the type of absorption study employed in this series, several points become apparent. The heights and shapes of serum iron tolerance curves, both stable and isotopic, vary greatly from person to person regardless of the initial fasting serum iron level or the hematologic picture (Figs. 1 and 2), but the shape of the stable and radioactive curves on single individuals are of generally similar contour.

Throughout all the studies the recovery of serum iron, stable or radioactive, was considerably less than the recovery in hemoglobin or the estimation of absorption by stool analysis. This is consistent with previous work in the literature,[1,3,4,13] and the reason for the difference has already been commented upon. As others have pointed out,[12] the administration of the large doses of iron necessary to study changes of stable iron in the serum is unphysiologic, whereas the minute quantity of elemental iron necessary for evaluation of absorption with a radioactive tracer allows a more physiologic procedure. It is interesting to observe in the present study that in the serum the recoveries of stable iron were generally more similar to the tracer recoveries when both iron salts were administered in the same state of reduction (or were reduced simultaneously from the ferric state) than when a ferric tracer was given with a large quantity of stable ferrous iron. As a ferrous tracer is now available, there is no reason to employ the large amount of reduced stable iron as a carrier or to rely on other reducing agents, such as ascorbic acid, for maximal absorption.

Since the serum recoveries are 30 to 40 per cent less than the later hemoglobin recovery of ingested iron, there is little value in carrying out the serum procedure, except in an attempt to evaluate the rapidity of iron absorption shortly after its administration. Such a study might be valid for healthy subjects, but in disease states no real evidence of total iron absorption can be obtained from serum or plasma measurements, as the rate of iron removal to storage tissues may vary widely.[14]

Accordingly, for the study of iron absorption in patients with various disease states the radioactive tracer technique, allowing evaluation of eventual iron uptake in hemoglobin and its total absorption by stool analysis, provides a more accurate and physiologic method. The stool analysis technique has been shown to be more reliable in the study of disease, however, because certain conditions, such as fever or infection, may impair the synthesis of hemoglobin and render the estimation of iron absorption by hemoglobin analysis unsatisfactory.[15]

SUMMARY

An iron tolerance test, employing both stable and radioactive iron, has been evaluated in a series of healthy controls and in a series of patients with a variety of disease. The data for hourly serum recoveries of iron over a four-hour period, later recovery in hemoglobin of radioactive iron, and estimation of total iron absorption by stool analysis of radioactive iron are presented for both series. The effect of reduction of iron to the ferrous state on its absorption has again been demonstrated, and the relatively poor absorption of ferric iron has been substantiated. By the present tolerance test, increased absorption in iron-deficient patients has been demonstrated. The relative inaccuracy of serum values as an indication of iron absorption has been emphasized, and it is concluded that a radioactive ferrous iron tracer technique provides a more useful and reliable measurement of iron absorption than does the stable iron tolerance test.

ACKNOWLEDGMENT

We wish to thank Dr. L. E. Hinkle and Dr. R. Engle for valuable advice and criticism.

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Pyruvate Metabolism in Obesity

By A. T. MILLER, JR., M.D.,* AND BARBARA M. THOMAS, B.S.†

IT IS generally agreed that obesity is the result of excessive caloric intake in the sense that caloric restriction corrects the condition. Opinions differ, however, concerning the cause of the overeating. According to the "orthodox" view,[1] most obese persons are metabolically normal, and obesity results from failure to curb the appetite. This concept has, from time to time, been challenged by proponents of theories attributing obesity to metabolic abnormalities.[2-4] In recent years, Pennington has vigorously advocated a theory which makes obesity the necessary consequence of a defect in intermediary metabolism.[5-10]

Pennington's thesis is that obesity-prone persons are characterized by an enzymatic defect in carbohydrate metabolism which results in the accumulation of excessive amounts of pyruvate. The pyruvate in turn depresses the oxidation of fat and increases lipogenesis from carbohydrate, with the result that an abnormally large proportion of both carbohydrate and fat is diverted to fat storage instead of being oxidized for energy. Then the appetite, regulated to supply the energy needs of the body, dictates the intake of an increased amount of food to compensate for the amount diverted to storage. The inhibition of fat oxidation by pyruvate lowers the rate of mobilization of fat, but eventually the increased size of the adipose depots makes possible the release of enough fat to supply the energy needs of the body. "Thus obesity might be considered as a compensatory hypertrophy of the adipose tissues, providing for an increased use of fat by an organism that suffers an impairment in its ability to oxidize carbohydrate."[8] Pennington has suggested, on the basis of this theory, that the logical treatment of obesity is not caloric restriction, but rather restriction of the carbohydrate precursors of pyruvic acid in a calorically adequate diet.

The basic assumption on which Pennington's theory rests is that pyruvate accumulates in excessive amounts in the blood and tissues of obese persons when their metabolic mixture consists largely of carbohydrate. This assumption has not been tested directly in human obesity. Pennington bases his claim on the indirect evidence of a greater exercise-induced rise in blood lactate in obese subjects[11] and of blood pyruvate in diabetic subjects[12] than in normal subjects, and on the elevated blood pyruvate of the hereditarily obese-hyperglycemic mice.[13]

The experiments to be described were undertaken in an effort to obtain information of a more direct nature. They are based on the assumption that a metabolic defect of the type postulated by Pennington should be exaggerated by any condition which increases the demand for the metabolism of carbohydrate. Two such conditions are exercise of brief duration and the ingestion of glucose.

EXPERIMENTS

Basal Levels

The basal blood pyruvate level was measured in 16 normal-weight and 16 obese hospital patients (Table I). The obese patients averaged about 40 per cent overweight according to standard weight tables. The degree of obesity for each group is expressed in each table as: Relative weight = (actual weight)/(ideal weight), so that, for example, a relative weight of 1.3 would indicate 30 per cent overweight. In preliminary studies the basal blood pyruvate level was found to be variably elevated in patients with liver disease, congestive heart failure, collagen diseases, malignancy, and in healing fractures.[14] Accordingly, no

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This work was supported by a grant from the Life Insurance Medical Research Fund.

TABLE I

Basal Blood Pyruvate Levels in Normal-Weight and Obese Patients

Normal-weight patients*					Obese patients†				
Diagnosis	Sex	Age	Relative wt.	Pyruvate *mg/100 ml*	Diagnosis	Sex	Age	Relative wt.	Pyruvate *mg/100 ml*
Functional uterine bleeding	F	29	0.7	0.95	Recurring right inguinal hernia	F	41	1.2	0.78
Glioblastoma multiforme	F	21	0.8	1.32	Spinal injury—quadriplegia	M	30	1.3	1.51
Ptosis, right kidney	M	23	0.8	0.90	Incisional hernia	F	44	1.3	0.92
Postpartum	F	26	0.8	0.63	Functional uterine bleeding	F	65	1.3	0.75
Eczema	F	17	0.8	0.75	Anxiety reaction	F	34	1.3	0.76
Postpartum	F	29	0.9	1.09	Cardiac enlargement	M	80	1.4	0.65
Patent ductus arteriosus, subacute bacterial endocarditis	M	19	0.9	1.30	Scar abscess of abdominal wall	F	40	1.4	0.8
Pyelitis, afebrile	F	22	0.9	1.23	Diabetes, hypertension	F	60	1.4	0.92
Pulmonary blastomycosis	M	23	0.9	1.29	Ruptured intervertebral disc	F	29	1.4	0.91
Postpartum	F	20	0.9	0.80	Fracture of right humerus 2 weeks previously	F	49	1.5	0.91
Bronchiectasis	F	61	1.0	1.11	Basilar artery thrombosis and essential hypertension	F	43	1.5	1.42
Sickle cell anemia	F	30	1.0	0.88	Chronic leg ulcers	F	50	1.5	1.10
Normal staff member	M	27	1.0	1.27	Multiple draining sinuses (staph. aureus)	M	34	1.6	0.65
Lung abscess	F	37	1.0	0.93	Dislocated elbow	F	25	1.8	1.19
Postpartum	F	33	1.0	1.35	Chronic leg ulcers	F	56	1.8	0.69
Postappendectomy	F	24	1.1	1.25	Postpartum	F	27	2.0	0.66

* Sex: males, 4; females, 12. Age: range, 17–61; average, 28. Relative weight: range, 0.7–1.1; average, 0.9. Blood pyruvate: range, 0.63–1.35; average, 1.07 mg/100 ml.

† Sex: males, 3; females, 13. Age: average, 44; range, 25–80. Relative weight: range, 1.2–2.0; average, 1.5. Blood pyruvate: range, 0.65–1.51; average, 0.91 mg/100 ml.

patients with these conditions, nor with fever, extensive drug therapy, or suspected vitamin deficiencies were included in the series.

Pyruvic acid,[15] lactic acid,[16] and glucose[17] concentrations were measured in blood obtained by venipuncture, without stasis and with rigid precautions for prevention of *in vitro* changes in these constituents. The average blood pyruvate levels were 1.07 ± 0.23 mg per 100 ml in the normal-weight patients, and 0.91 ± 0.25 mg per 100 ml in the obese patients. The difference between the two groups is not statistically significant. Most of the patients were in a state of "static" obesity, but there is no reason to believe that cessation of active weight gain would result in the disappearance of an abnormality of intermediary metabolism if one existed. It may therefore be concluded that there is no evidence that blood (and presumably tissue) pyruvate concentration is elevated in obese persons under basal conditions.

Pyruvate Levels after Glucose

It may, however, be argued that pyruvate would accumulate in obese persons only when the demand for metabolism of carbohydrate is increased. In order to test this possibility, blood pyruvate levels were compared in obese

TABLE II

Comparison of Blood Pyruvate Rise in Response to Glucose Administration in Normal-Weight* and Obese† Subjects

	Subjects	Time after glucose: Control	30 min	60 min	90 min	Maximum rise
Blood glucose, mg/100 ml	Normal	86 (60–99)	139 (104–164)	134 (75–164)	111 (62–170)	53 (24–98)
	Obese	74 (50–89)	109 (76–134)	114 (89–137)	97 (80–111)	40 (30–64)
Blood pyruvate, mg/100 ml	Normal	1.16 (0.75–1.60)	1.36 (1.10–1.70)	1.50 (1.23–2.03)	1.32 (0.90–1.80)	0.34 (0.11–0.76)
	Obese	1.12 (1.00–1.48)	1.30 (1.19–1.69)	1.39 (1.19–1.65)	1.27 (0.97–1.39)	0.27 (0.14–0.59)

* Relative weight: range, 0.9–1.1; average, 1.0.
† Relative weight: range, 1.2–1.9; average, 1.5.

TABLE III

Blood Glucose, Pyruvate, and Lactate Responses to Exercise in Normal-Weight* and Obese† Subjects

	Subjects	Time after exercise: Control	2 min	30 min	Maximum change
Blood glucose, mg/100 ml	Normal	81 (72–88)	62 (51–81)	76 (72–95)	−19 (+4 to −37)
	Obese	99 (86–109)	92 (68–112)	83 (58–119)	−16 (+14 to −40)
Blood pyruvate, mg/100 ml	Normal	1.20 (0.53–1.75)	3.02 (2.25–4.35)	1.75 (1.15–3.15)	1.82 (0.63–2.85)
	Obese	1.49 (0.93–2.07)	4.93 (3.59–6.23)	3.99 (2.58–5.87)	3.44 (1.78–4.91)
Blood lactate, mg/100 ml	Normal	12 (8–23)	58 (22–89)	19 (11–35)	46 (11–75)
	Obese	16 (10–24)	121 (92–172)	58 (35–85)	105 (79–148)

* Relative weight: range, 0.8–1.1; average, 1.0.
† Relative weight: range, 1.3–1.9; average, 1.6.

and normal subjects following (a) the ingestion of 50 grams of glucose, and (b) strenuous muscular exercise. The subjects used for the glucose tolerance and exercise studies were (with one exception) different from the hospital patients on whom basal blood pyruvate levels were measured.

It has long been known[18] that the ingestion of glucose is followed by a rise in the blood pyruvic acid concentration, presumably due to failure of the oxidation of pyruvate via the Krebs cycle to keep pace with the rate of its formation by glycolysis. If this failure is more marked in obese persons, as postulated by Pennington, the rise in blood pyruvate following glucose administration should be correspondingly exaggerated.

In preliminary tests in normal and obese subjects, it was found that the oral administration of 50, 100, and 150 grams of glucose caused about the same peak rise in blood pyruvate, although the pyruvate rise was more sustained with the larger doses of glucose. Accordingly, all subjects were given a standard dose of 50 grams of glucose as a 25 per cent solution in tea. The subjects were in a postabsorptive state and had rested in bed for one hour before the administration of glucose. Blood glucose and pyruvate concentrations were determined 30, 45, 60, and 90 minutes following glucose ingestion (Table II). The peak pyruvate rise usually occurred at 60 minutes, though occasionally at 30 or 45 minutes. In all cases, the blood pyruvate level was falling at 90 minutes. The average peak rise in blood pyruvate was 0.34 mg per 100 ml in eight normal subjects (range 0.11–0.76), and 0.27 mg per 100 ml in six obese subjects (range 0.14–0.59).

The time at which the peak rise in blood pyruvate occurred was not consistently different in the two groups of subjects.

Pyruvate Levels after Exercise

The blood pyruvate rise induced by the increased metabolism of endogenous carbohydrate during exercise was compared in normal and obese subjects. About one hour following the usual midday meal, the subjects rested in bed for 30 minutes and then ran at 7 miles per hour for 7 minutes on a motor-driven treadmill. Blood samples were obtained before the exercise, and 2 minutes and 30 minutes after exercise. Analyses were performed for glucose, pyruvic acid, and lactic acid (Table III). On another day, each subject was given a standard cardiovascular fitness test (the Harvard Step Test). The blood pyruvate concentration was always greater 2 minutes after exercise than it was 30 minutes after, and the former value was accordingly used for the peak response. The postexercise rise in blood pyruvate averaged 3.44 mg per 100 ml (range 1.78–4.91) in six obese subjects and 1.82 mg per 100 ml (range 0.63–2.85) in six normal subjects. The greater postexercise blood pyruvate rise in the obese subjects was proportional to their greater postexercise blood lactate rise (103 mg per 100 ml in the obese, and 44 mg per 100 ml in the normal subjects), and inversely proportional to their lower cardiovascular efficiency as measured by the Harvard Step Test scores (39 in the obese and 82 in the normal subjects), Figure 1.

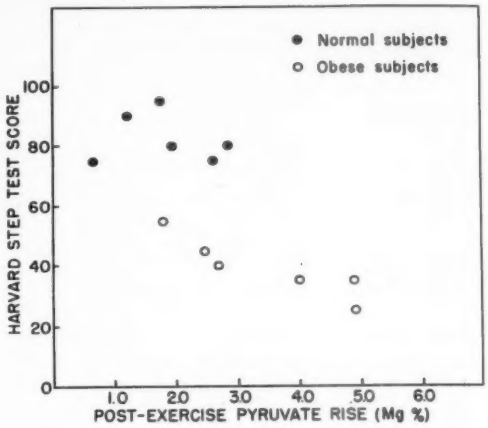

Fig. 1. The relation between postexercise blood pyruvate rise and cardiovascular fitness (Harvard Step Test score) in normal and obese subjects.

It seems probable, therefore, that the greater postexercise rise in blood pyruvate (and of blood lactate in the experiments quoted by Pennington) in the obese subjects reflects their less efficient cardiovascular response to exercise rather than an abnormality in carbohydrate metabolism. In the normal subjects, the blood glucose values immediately after exercise were consistently about 20 mg per 100 ml lower than the resting values. In the obese subjects, the postexercise glucose changes were extremely variable, with a tendency toward a smaller decrease than in the normal subjects. Whether this represents a less efficient mobilization of glucose or a more rapid utilization cannot be decided on the basis of these data alone.

DISCUSSION

The administration of glucose increases its rate of utilization;[19] since blood pyruvate also increases, it would seem that the rate of glycolysis may readily exceed the rate of oxidative removal of pyruvate. The initial increase in the blood levels of pyruvate and lactate during moderate exercise is apparently due, at least in part, to an inadequate provision of oxygen for maintaining the oxidative removal of pyruvate, because the achievement of a steady state stops the further accumulation of pyruvate.

The fact that the blood pyruvate rise in response to glucose administration is of about the same magnitude in obese and normal subjects indicates that the oxidative removal of pyruvate is probably no less efficient in obese than in normal subjects. In addition, a reduced rate of oxidative decarboxylation, by decreasing the formation of acetate from pyruvate, would probably reduce the rate of lipogenesis from carbohydrate, instead of increasing it as claimed by Pennington.

If there is no impairment in the enzymatic reactions involved in the disposal of pyruvate in obese persons, it is probable that the greater

postexercise rise in blood pyruvate is due either to a higher rate of glycolysis because of the greater energy cost of exercise[20] or to a less adequate oxygen supply due to the less efficient cardiovascular adjustment to exercise. Prodger and Dennig[11] believed that the greater post exercise rise in blood lactate in their obese subjects was not due to circulatory inadequacy. Their point is not well taken, however, since their data indicate that exercise resulted in a greater oxygen debt and a greater increase in arteriovenous oxygen difference in the obese subjects. Both of these results indicate less adequate blood flow through the working muscles.

Pennington[21] has recently speculated on the most likely site at which a block in pyruvate metabolism might occur. Using the obese-hyperglycemic mice as the prototype of human obesity, he reasons that, since the obese mice are able to oxidize fat,[22] the pathway of fat breakdown and its entrance, by way of acetyl coenzyme A, into the Krebs cycle must be intact. "The metabolic fault in this form of obesity, therefore, must lie at a point above the level of acetyl CoA; it must be looked for somewhere between pyruvic acid and acetyl CoA."[21] The specific defect, according to Pennington, may involve the enzyme lipoic acid conjugase, which is essential for the formation of the coenzyme lipothiamide pyrophosphate (LTPP). There is evidence that LTPP is necessary for the transfer of the acetyl group (derived from pyruvate) to coenzyme A to form acetyl coenzyme A, the form in which metabolites enter the Krebs cycle.[23]

Pennington's speculations are open to serious question. Not only do the genetically obese mice differ from obese humans in important respects, but the claim that the obese mice have a defective capacity for oxidizing administered acetate[13] has not been confirmed.[24] Furthermore, Pennington's claim that the formation of the coenzyme LTPP is easily impaired is based on the fact that the enzyme lipoic acid conjugase is absent in a mutant strain of *E. coli*,[25] surely a far cry from the problems of human obesity.

Since the pyruvic oxidase system is almost selectively inhibited by very small amounts of arsenite,[26] it would seem that the concept of a block in pyruvate metabolism as the cause of obesity should be susceptible of experimental verification. Studies based on this idea are being undertaken in this laboratory. Another approach might be to test the effects on glucose oxidation of the addition of purified lipoic acid conjugase to tissue homogenates from obese and nonobese mice.

SUMMARY AND CONCLUSIONS

One explanation for the pathogenesis of obesity is Pennington's theory based on a postulated block in carbohydrate metabolism at the pyruvate level. Experiments to test this hypothesis were performed in 16 normal-weight and 16 obese subjects.

It was found that the basal blood pyruvate level is not elevated in obese subjects. The oral administration of 50 grams of glucose is followed by a similar rise in blood pyruvate concentration in both normal and obese subjects. Moderate exercise causes a greater rise in blood lactate and pyruvate in obese than in normal-weight subjects. Reasons are given for attributing this result to circulatory inadequacy rather than to metabolic abnormality.

The application of these results to Pennington's theory of obesity is discussed. It is concluded that no direct evidence exists in support of Pennington's basic postulate of a metabolic defect resulting in the accumulation of excessive amounts of pyruvate in the blood and tissues of obese persons.

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The Care and Nutrition of a Patient in Prolonged Coma

By RALPH L. HOPP, M.D.,* W. J. A. FORD, M.D.,† and S. J. O'CONNOR, M.D.‡

ALTHOUGH about three per cent of all hospital admissions are due to coma, it is unusual for the coma or stupor to last for a long period of time. We have been caring for a patient who has been unresponsive for more than 17 months. To maintain such a patient in adequate nutrition and health presents many problems. Some of the broader concepts of this management and the case history, which illustrates these concepts, are presented.

GENERAL MANAGEMENT

Regardless of the cause of the coma, comatose patients frequently die from anoxia. Occasionally, the patient may be able to maintain adequate aeration but usually, because of tongue retraction, poor positioning of the head, and increasing pharyngeal and tracheal secretions, anoxia occurs. Frequently, an oral airway and nasopharyngeal suction are inadequate as secretions collect beyond the reach of the catheter. Intratracheal intubation requires the technical skill of trained anesthetists and the tube must be changed and cleaned every 24 hours, thereby increasing laryngeal and tracheal edema. Tracheotomy is superior to any other method of maintaining efficient aeration of the lungs and keeping a tracheobronchial tree free of secretions. If the patient shows any signs of respiratory distress or if coma persists more than 48 hours, a tracheotomy should be done.[1,2]

The head of the bed should be elevated 30–45° and lowered for 15 minutes every one to two hours to facilitate removal of secretions. This position favors cerebral venous return, allows a fuller excursion of the diaphragm, and permits more adequate ventilation of the lungs.

Adequate suction, administration of oxygen, preferably humidified to prevent drying of tracheobronchial tree, and avoidance of respiratory depressant drugs are important adjuncts. Since convulsions increase bronchial secretions, they should be controlled with barbiturates, administered intravenously if necessary, or with chloral hydrate. If nasal oxygen is given, the tube should be checked frequently for even partial plugging.

The abnormal static position of the comatose patient and the inability to cough and breathe deeply are factors conducive to atelectasis and pulmonary infection. In addition, this immobility favors the formation of decubitus ulcers, contractures, and degenerative joint changes, as well as venous thrombosis of the extremities.

Positioning of the patient as described, turning from side to side every two hours, tracheobronchial suction, skin massage, and passive exercises, in which all joints are moved through a complete range of motion many times daily, will prevent almost all of these debilitating sequelae. The bed must be kept dry and the sheets removed properly to prevent sheet burn. "Doughnuts" around pressure areas are to be condemned as they retard circulation, but bridging on each side of the pressure area may be used.

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Fecal impaction with distention and diarrhea is the principal bowel problem. A rectal examination should be performed at least every three days, and enemas and mild cathartics administered as needed.

Urinary retention, infection, and stone formation are frequent complications in patients who are bedfast. A Foley catheter should be inserted and attached to an intermittent bladder irrigator with Suby-Albright solution or a mild antiseptic irrigating solution. The catheter should be changed every 10 to 30 days and antibiotics used as indicated. An adequate urinary output must be maintained to prevent stone formation due to the mobilization of calcium and phosphorus from the bones. Marshall and Green[3] report that a diet low in phosphorus and aluminum gel by mouth will decrease the urinary output of phosphorus. Since two-thirds of all urinary calculi in the bedfast patient are of the phosphate variety, a low urinary excretion of phosphorus is desirable. Dietary calcium need not be restricted.[4]

Corneal drying, ulceration, and perforation should be prevented by using the following measures: (1) some form of modified tarsorrhaphy so that the eye can be examined easily, such as Scotch tape to close the lids or silk suture through the upper lid and taped to the cheek; (2) the use of methylcellulose drops $^1/_2$ per cent, during the day and mineral oil drops at night to prevent drying; (3) antibiotics as indicated; (4) staining of the cornea twice a week to detect ulceration

HYDRATION AND NUTRITION

There are two major practical routes by which nutrients may be administered to the comatose patient: intravenous and nasogastric tube feeding. The basic minimum daily requirement of the average adult at bed rest consists of a diet containing approximately 70 g protein and 2400 calories, 30 per cent as fat, in addition to vitamins and minerals.[5]

In order to maintain this requirement by the intravenous route, at least 3000 ml of a 5 per cent protein hydrolysate in 10 to 15 per cent glucose solution must be given daily.[6] Whole blood, plasma, and alcohol have been recommended as supplements, but 500 ml of whole blood will supply only 17.5 g of proteins and 70 calories.[6,7] Alcohol, which supplies calories only, should not be given to the unconscious patient.[8] Although it is possible to maintain a patient in positive nitrogen balance for a short period of time by intravenous feeding, more than twice as much nitrogen is required with the same caloric intake.[9,10] Of course, the intravenous route is limited by the veins available and by the skill of the house staff and nursing care.[9]

In the first 24 to 72 hours, the intravenous route is preferred to supply adequate fluid, blood, and plasma, but after that time tube feeding should be instituted. Different commercially available formulas have been advocated for tube feeding.[11,12] These formulas contain milk or milk powder, sugar and protein; vitamins are added as necessary.

Barron and Fallis[13] believe that no commercially prepared formula can replace natural food and recently reported their experience in the tube feeding of 200 patients. By the use of a blendor or liquefying machine, whole food was converted to a liquid and injected into the stomach with a feeding pump through a small 2.5-mm plastic tube. This diet was well tolerated and 1300 calories could easily be included in one liter of fluid. Barker[14] agrees that it is an ideal feeding mixture.[14]

Distention and diarrhea have been a minor but constant side-effect from tube feeding of a formula. Elman and co-workers[11] reported an overall incidence of 5 per cent, with discontinuance of tube feeding necessary in 2 per cent of 316 patients. Others report an incidence of up to 39 per cent.[5] That diarrhea is a rather constant feature is illustrated by the frequent suggestions for the use of Banthine (brand of methantheline bromide), paregoric, pectin, etc., for its temporary control.[15,16] Diarrhea did not occur, however, with liquefied whole food.

Rarely have cases of tracheo-esophageal fistula been reported when an orogastric tube and tracheal cannula were used together.[17] Fallis and Barron,[18] using small polyethylene

TABLE I

Laboratory Studies on a Patient in Prolonged Coma

Determination	1954			1955	
	8/23	9/3	12/23	5/9	11/5
Hemoglobin (g/100 ml)	6.4	12.5	12.1	16.2	15.1
Nonprotein nitrogen (mg/100 ml)	69.5	61.0	26.9	29.5	29.0
CO_2 (vol/100 ml)	76	69	68	73	—
Chlorides (meq/liter)	104	108	—	104	99
Potassium (meq/liter)	4.9	5.5	5.5	—	5.3
Sodium (meq/liter)	145	146	137	143	132
Total proteins (g/100 ml)	—	—	7.13	7.6	7.43
A/G Ratio	—	—	0.84/1	1.03/1	1.2/1

tubes, found no irritation from the tubes after many months' use. McNeer thought that more frequent pulmonary complications occurred, but Pack and others do not agree.[14]

It is important that the feedings be given as a constant slow drip or at spaced intervals to prevent vomiting and aspiration due to gastric distention. It also should be noted that azotemia, hypernatremia, and hyperchloremia may occur if an insufficient amount of fluid is given with a high protein diet.[19]

We are reporting our experience with a patient who was admitted to this hospital in August 1954 because of a fall and multiple fractures. He became comatose on the same day after occurrence of fat embolism. Maintenance of nutrition has been accomplished with homogenized whole food, and physiotherapy has prevented all of the complications inherent in the prolonged bed rest. His nutritional status has improved and his condition remains excellent after *more than 17 months of coma*.

CASE REPORT

R.S., a 37-year-old colored man fell two stories on August 20, 1954, and landed on his left leg and side. He was brought immediately to the emergency room of the hospital, and at that time was completely conscious and co-operative. There were obvious closed fractures of the left leg and hip, as well as tenderness in left flank and costovertebral angle. In the absence of head injury, 15 mg of morphine was given for pain. Roentgenograms revealed comminuted fractures of the left tibia, fibula, and subtrochanteric area of left femur.

The patient was placed in balanced traction with a Kirschner wire through the lower tibia. He became progressively stuporous and 11 hours after admission could not be aroused. At that time, the blood pressure was 170/120 mm Hg, pulse, 110 per minute, and respirations, 36 per minute. His hemoglobin, which had been 12.8 g on admission had dropped to 11.4 g per 100 ml. He was seen by a general surgeon for possible intra-abdominal injury and by a neurosurgeon for the cause of coma. Fat embolism was suggested and urinalysis revealed large amounts of fat. A Foley catheter was inserted and attached to an intermittent bladder irrigator. Antibiotic therapy was started.

An oral airway was introduced and humidified oxygen was given through a nasal catheter. Because of accumulating secretion and increasing respiratory difficulty, a tracheotomy was done the following morning with respiratory improvement. Although he remained critically ill for the next two weeks, his vital signs gradually returned to within normal limits. During this time, he received nine pints of blood and intravenous fluids totaling 3000 ml daily in order to maintain an adequate urinary output and normal electrolyte balance. He received an average of 650 calories a day.

Two weeks after admission, a nasogastric polyethylene tube was inserted and formula feeding was started. He received 126 grams of protein, 142 grams of fat, 336 grams of carbohydrate, and 3000 calories in 2400 ml. Oxygen could be discontinued on the 27th day. The patient's arms and right leg were moved through a complete range of motion every hour and the patient was turned every two hours. Four months after admission, balanced traction was discontinued and skin traction applied for an additional month.

Four and one-half months after admission, a liquefied general diet was started. A regular diet was liquefied with a Waring blendor, after removal of bones and seeds, and liquids were added as necessary. From 100 to 200 ml of the liquefied diet is given every hour through the tube. The diet he is now receiving furnishes 2400 calories, 20 to 25 per cent as fat, with 70 grams of protein, and 3000 ml of fluid daily.

Although the patient manifests decerebrate rigidity, he is lifted into a chair daily and has no contractures. He has not had pneumonia at any time and has no evidence of urinary tract stones. The urinary output is adequate. He has been on a homogenized regular diet for more than a year and has had no diarrhea.

Although Zintel[20] states that patients do not often improve on formula feeding, we find that in this case the patient's total protein and hemoglobin concentration have improved (Table I). We believe that for long-term feeding by the nasogastric route, a homogenized general diet will provide the ideal feeding mixture.

SUMMARY AND CONCLUSION

We have briefly outlined the care and nutrition of the patient in prolonged coma, a subject about which little can be found in the literature. We believe the following points should be emphasized:

(1) Tracheotomy should be performed in all patients who show signs of respiratory difficulty or who remain in coma over 48 hours.

(2) Intravenous blood and fluid should be administered until the patient has passed the initial critical phase of his illness, at which time nasogastric tube feeding should be begun if that route is available.

(3) Tube feeding with liquefied whole food is superior to other types of feeding formulas; it is easy to prepare, is well tolerated, has fewer side effects, and needs no supplementation.

An illustrative case history of a patient who has now been in coma for 17 months has been presented. We realize that his prognosis is hopeless, but he demonstrates what can be done to maintain a patient in prolonged coma in good physical condition.

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The Nutrition of Isolated Cells from Vertebrates

By PHILIP R. WHITE* PH.D

I HAVE BEEN asked to open this conference on "Optimal Nutrition" with a discussion of the subject as it applies to the fundamental physiological unit of all vertebrate (and other) life, the cell. This is one of the major problems of what we have come to call "tissue culture." Presumably I, as a tissue culturist, have been asked to speak on this subject because the nutrition of any organism is, after all, basically the sum total of the nutrition of its parts. Although we must never lose sight of the fact that what we are seeking is an eventual integration of all these parts into a well balanced whole, we must know what factors, in terms of individual cells, may tend to throw that whole out of balance.

DIFFERENTIAL NUTRITION

What is "optimal nutrition"? Optimal for what? For growth, for maintenance, for specific function? The thyroid concentrates iodine, the pancreas zinc, the liver copper and iron, the stomach lining cobalt. If we isolate the cells from these four types of epithelium should we expect that the optimal nutrition for all four will be the same? I hardly think so. The different layers of the adrenal are thought to manufacture each a different series of steroid compounds. Do these represent different synthetic capacities (hence different nutritional requirements), or do they, on the other hand, represent differences in the nutrition available to these cells, due to differential screening of the supply? The pituitary was once looked upon as a complex gland, but it has more recently become clear that removal of the pituitary does not eliminate all of the pituitary hormone effects, but only distributes those effects. The suspicion has arisen that the "gland" may not be the original source of all these hormones but rather a storage organ where they can be stock-piled for release in more massive quantities. If the former view is valid, then the different parts of the pituitary will have different "optimal nutrition" requirements. If the latter is true we must look to some stem tissue elsewhere as the really critical point.

These are not idle questions. One of the most dramatic demonstrations of their pertinence comes recently from Dr. Fell's laboratory in England.[1] There are in the body a great many different sorts of "epithelium." The skin is largely a protective layer and as such is thickened, keratinized. The lining of the intestine is a secretory layer as well as an absorptive one, and, as such, keratinization would interfere with its function. It is, rather, a simple columnar epithelium of glandular cells. Still a third type occurs in the lungs and nasal mucosa, where secretory function is coupled with a mechanical role in the ciliated layers. The cells originating in these three layers can all be grown in tissue culture, and if they are maintained in the usual nutrients they will all eventually take on a pattern resembling the intestinal cells. But if they are nourished with serum taken from animals, usually birds, which have been reared on a low vitamin A diet, so that they are deficient in this respect,

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Presented at the *Conference on Optimal Nutrition, Its Analysis and Application,* held at the George Williams College, Chicago, Ill., April 8–9, 1955.

the secretory function regresses and keratinization sets in. If, on the other hand, the serum is artificially fortified with excessively high vitamin A levels, there will be first a marked development of secretory function under the keratinized layers, these latter will be sloughed off, and eventually certain cells will develop active cilia, as well as accumulating mucous. The type of epithelium developed is thus sharply dependent on the amount of vitamin A available to the cells. The particular morphology of a given organ may be determined by the distribution of such substances in the body. At this level, at least, specific cell type is not internally but externally determined. The same holds true for bone. An excised femur can be caused to disintegrate into an amorphous mass of quite healthy chondroblasts without a trace of ossification, merely by increasing the level of vitamin A available to it.[2] "Optimal" nutrition can obviously be a very specific and highly localized affair!

Unfortunately, this work of Fell and Mellanby has only opened for us a tiny window into the vaults and chambers of nutritional morphogenesis. Vitamin A just happens to be one of the few substances for which we have recognized a specific formative function and which can at the same time be successfully manipulated in the simple fashion required by our present rather crude techniques. I am sure that there are many, many others. One may safely predict that the whole range of internal secretions will prove to have just such functions. I am equally certain that we need not turn to substances as complex as the hormones for examples.

WOUND HEALING

I will cite one from the woefully small number for which we have real data. It again involves epithelium. The healing of a wound involves two processes which are partly in sequence, partly concurrent. The bulk of the wound must be drawn together and filled in by fibroblast activity, by the formation of granulation tissue. And this granulation tissue must be covered by epithelium. The first starts from the depths of the wound, the second from its margins. If the growth of epithelium nearly or quite keeps pace with granulation the wound will heal with little or no scar. If epithelialization lags, the granulation tissue becomes more and more massive and irregular and difficult to cover. If covering is not complete, we have a persistent ulcer. Consequently it is of the utmost importance to stimulate rapid growth of epithelium and to hold back fibroblast activity at least to the point of balancing the two. What then distinguishes between the two types of growth? Parshley and Simms, at Columbia College of Physicians and Surgeons, set out to define these differences.[3] It develops that in a culture consisting of a mixed colony of human epithelium and fibroblasts, one of the things which will favor the development of epithelium is to increase the available phosphate concentration of the nutrient, at the same time reducing the calcium level. One can end up with pure epithelium, or pure connective tissue, or a mixed colony by adjusting the phosphate and calcium levels in the nutrient. Phosphate is chemically a lot simpler than is vitamin A! But unfortunately it is not so easy to control the local supply of phosphate to a specific area of the body, the wounded area, without also affecting other areas. The body itself has some rather effective mechanisms for controlling this general level, which mechanisms will be difficult to overcome. This study has *not* led to clinical applications. Scientifically, the way has been pointed out—but technically it is still beyond our present capacities to do anything about it!

TISSUE CULTURE STUDIES

I cite these few examples largely to establish a framework. While you may perhaps *hope* that I will talk about *your* problems I am sure you do not expect me to ignore my own. Each of us has his hobby horse. Mine is cell nutrition *outside* the body, in tissue culture. So I am sure you will allow me a brief canter over the fields which lie open to me.

How do we go about studying cell nutrition? Obviously by isolating a cell and then controlling its nutrition. To what extent can we do this? The classic tissue culture nutrient for connective tissue consists of 40 per cent serum

—chick or rabbit serum if you prepare your own, horse serum if you buy it, human placental cord serum if you are attached to a big hospital, plus 20 per cent embryo-extract—again chick embryos or beef embryos if you prefer, plus 40 per cent of a balanced salt solution. One can control what goes into the salt solution. That is no problem. One may exert some slight control over the serum by choosing the nutritional background of the chickens or horses from which it is derived as Fell and Mellanby did (but what control do those who use placental cord serum have over the nutritional history of *their* sources?) and one can exert little or no control over the nutritional content of the embryo-extract. Fell and Mellanby did a masterful piece of nutritional work in their vitamin A studies, but against what odds! The classic method is simply not designed for that kind of thing! Baker and Carrel, Ebeling, Fischer, and a few others have tried to analyze serum and embryo-extract. But the 40:20:40 formula still stands as standard for most work.

Ten years ago I set out to try my hand at correcting this state of affairs. Over the past quarter century there has grown up a large literature on the nutrition of protozoa, bacteria, yeasts, fruit flies, dogs—and *Homo sapiens*. It is a motley literature, but certain patterns keep recurring. A considerable number of elements are required by all and can be supplied by the same salts. The fact that snails have copper in place of iron in their hemoglobins, while vanadium is the replacement in certain tunicates, are exceptions to the general rule. The fruit fly—*Drosophila*, the protozoan—*Tetrahymena*, and the mammal—*Canis domestica* all require for maintenance the same eight amino acids plus, in each case, certain others which are more specific. All organisms require certain vitamins. One is by no means working entirely blindly when he goes to the chemist's shelf and takes down this bottle, and this, and this, to *build* a nutrient, though he obviously risks the chance of missing some crucial substance which may mask the effectiveness of all the rest. In 1946 I published one such mixture which would support contraction of chick heart muscle for about 40 days, as against 5 or 6 days in a simple balanced salt-dextrose solution.[4] In 1949 I improved this by addition of four more amino acids, doubling the survival of cells.[5] More recently, Dr. Waymouth has improved the result greatly by simply trebling the level of phosphate-bicarbonate buffer.[6] These defined nutrients did not support prolonged *growth* of tissues, but only survival and metabolic maintenance. More recently we have taken the step which every experimenter must make periodically, going back to see just what we have accomplished in terms of improving the classic approach.

The defined portion of the classic nutrient was confined to the balanced salt solution. What would happen if, for this balanced salt solution, we substituted one of our more complex defined nutrients and then tried progressively reducing the concentrations of the remaining unknowns? This we have done, using one of Earle's single-cell strains of mouse cells as test organisms.[7] I cannot generalize as to other types of cells, but it is highly probable that such generalization will eventually prove possible (Table I).

In the first place embryo-extract is *not* necessary for rapid growth of these cells. For about a year now we have maintained our stock cultures without any embryo-extract at all. They grow almost if not quite as fast as in the classic nutrient—quite fast enough for all routine purposes. In the second place, the serum level can also be drastically reduced. Routinely, we still maintain a 5 per cent level of serum in our stock cultures, as compared to the 40 per cent in the classic formulae, with 95 per cent of a defined nutrient. This *can* be still further reduced. In a 2:98 per cent nutrient, Strain L cells grow very slowly, so slowly that it takes 6 to 8 weeks to reach a level of cell density sufficient to justify subculturing, as against the 8 to 10 days which cultures in a 5:95 per cent nutrient require for the same growth. In a 1:99 per cent nutrient the same cells multiply just enough to balance cell losses, and a colony will have about the same density at the end of

TABLE I

Defined Maintenance Nutrient for L-Strain Mouse Cells

The control nutrient (W11) contains the following final concentrations in milligrams per liter:

Fructose	8500	Glycine	100
NaCl	7000	Cysteine HCl	1
KCl	375	Glutathione	1
$MgSO_4$	275	Thiamine	1
$Ca(NO_3)_2.H_2O$	210	Riboflavin	1
$NaHCO_3$	1102.5	Ca-pantothenate	1
Na_2HPO_4	115	Pyridoxine	5
KH_2PO_4	52	Nicotinic acid	5
$Fe(NO_3)_2.9H_2O$	1.375	*i*-Inositol	5
L-Cystine	7.5	β-Alanine	5
L-Glutamic acid	140	Choline HCl	10
L-Aspartic acid	60	*d*-Biotin	1
L-Leucine	156	Folic acid	1
DL-Isoleucine	104	Ascorbic acid	0.5
L-Phenylalanine	50	Vitamin A	0.1
L-Methionine	130	β-Carotene	0.1
L-Threonine	130	Vitamin B_{12}	0.025
DL-Valine	130	Phenol red	4
L-Lysine HCl	156	Ethanol	1
L-Arginine HCl	78		
L-Histidine HCl	26		
L-Proline	50		
L-Tryptophan	40		

8 weeks as at the beginning, although mitoses are still not uncommon. In a 0:100 per cent nutrient—that is, one in which only ingredients off the chemical shelf are used—no growth occurs and there is a gradual loss of cells, yet cultures kept in such a solution remain viable for many weeks, and will resume normal growth within a matter of hours when transferred to a 5:95 per cent nutrient. We have not quite attained our goal of being able to define *all* the requirements for cell growth, but we are certainly approaching it.

Perhaps some of you will say "But this goal *has* already been attained, in Parker's nutrient #703."[8] I should not wish to deny that. But I would remark that the formulae with which we in this Laboratory are working contain less than half the number of ingredients of #703. And many of those omitted are among the very expensive ones—the co-enzymes for example. We are aiming at simplicity as well as definition—something that can eventually be put into the hands of little laboratories as well as big ones. That is not an impossible goal. One of our most spectacular improvements came from changing the buffer concentration—something that one might have supposed was pretty well established!

OBJECTIVES

When we attain this preliminary goal, and only then, can we hope to attack on a rational and really hopeful basis, some of these critical problems: how to supply the optimal nutritional conditions to a healing wound; how to overcome resistance to skin and gland transplants; how to promote the growth of a severed nerve before the surrounding fibroblasts can penetrate the sheath and turn the nerve back upon itself, as now so often happens; how to encourage a damaged gland to resume its function without tipping it over into a state of malignancy; and, by no means least, how to encourage a none-too-perfect brain to attain the highest functions of which it is inherently capable! Nutrition can be optimal for function, or for repair, for growth or for maintenance, or for eventual regression in unwanted members. Each will have unimagined complexities, once we can strip off the irrelevant and get down to facts. When we can tell you, from laboratory studies, what is the optimal nutritional background for each type of cell in the body at each stage, and for each of its normal and abnormal functions, we can give you the information with which to rear and maintain a perfect body. Holmes' "Deacon" had those secrets. We may search hopefully for them.

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Vitamins: Haves and Have-nots

"The need for vitamins of various animals and the ingenious way in which they are supplied make a truly fascinating study. For example, we know that the hervivora make their own B group vitamins in the rumen and/or series of stomachs with which many of them are supplied. The carnivora on the other hand have no rumina and no such ability and are therefore dependent on their own prey to supply their needs. One of the most curious facts recently brought to light is the way in which the rabbit supplies its needs for vitamin B. This, it would appear, is made largely in the caecum and colon. It is passed during the night as 'night soil' and reingested by the rabbit the following morning. From the current issue of *Family Doctor* we learn that 'Guinea pigs and men and apes are the only animals that need to have vitamin C in their food. All the other animals can make their own vitamin C.' One is not surprised to learn that man needs to have almost everything given him; he seems able to synthesise almost nothing but a little vitamin B in his intestine, and that amount is clearly not enough for his needs judging by the alacrity with which, given half a chance, he develops beri-beri. Our cousins, the monkeys, one is not surprised to learn, fall into the same category. But what about the guinea pig? Why should he be unable to do what the rabbit, the ox, the horse, the dog, the cat and all the rest including even the lowly mouse can manage? What factors in his evolutionary background have brought this about? He must have gotten his C *gratis* at one stage. How and when was that?"
—*Med. Press* 235: 456, 1956.

A Concept of Optimal Nutrition

By W. A. KREHL, PH.D.*

IMAGINE living without physical or emotional stress—no worry, no anxiety, no harrassment—life with complete freedom from want. Such a life would be lived in an environment of constant temperature at about 25° C, of filtered, humidified, properly oxygenated air free of pathogenic micro-organisms and all noxious gases. Patterns of movement, sleep, sex, and eating would all be strictly regulated and limited to prevent trauma. All needs would, of course, be provided without work, and everyone would be free and equal. There would be no keeping up with or getting ahead of the Joneses. Such a Utopia would be most unsavory, because it would be vegetative and without stimulation.

The price, then, of the verve, excitement, and enjoyment of life, which we all experience, brings with it many stresses, both exogenous and endogenous. Consider the case of Mr. X. He is a real dynamo—an ambitious, hard-driving fellow in the thick of things in his job and in the social whirl of the community. He is "going places," even though with every promotion the accompanying increase in salary is swallowed up by the ever increasing demands for the maintenance of social position. In order to keep up the pace, Mr. X may gradually increase his use of stimulants of various kinds and he looks fondly toward the end-of-the-day cocktail hour, which he welcomes for its pause of relaxation and the warmth of social amenities. Occasionally and increasingly often this cocktail hour stretches out into a long evening of drinking. At last, when ready for bed, exhausted, but still agonized by the tensions of the day, Mr. X may require the use of a barbiturate or sleeping potion to finally ease his busy mind and taut nerves into blissful sleep.

In addition, we find Mr. X eating too many big lunches and stuffing himself at too many dinners, and spending too little time on exercise. The gradual inevitable lengthening of the belt-line finally gives way to the full-blown battle of the bulge.

Despite this wear and tear, Mr. X says he feels well and, in fact, boasts a bit about having just passed a life insurance examination, although the doctor warned him that he had better slow up a bit and take off some weight.

The real threat of the type of stress that Mr. X is constantly exposed to is the insidious character of its slow, day-to-day process of attrition, with the gradual development of disorders without the revelation of noticeable danger signals. Oftentimes the frank signs and symptoms of pathologic damage are delayed until impairment of health is far advanced. The dramatic and sudden stress of trauma and exposure, on the other hand, is far less frequent and more easily coped with, especially by individuals who have maintained their body's natural defense mechanisms.

The unceasing efforts of the nutritional biochemist have been directed toward the development of ways and means by which man can employ nutrients alone and in various combinations to maintain his health and his natural resistances or defense mechanisms at the peak of their operational efficiency. At the same time, there has also been developed the concept that nutritional correction can do much to repair the injuries induced through nutritional sins of omission and commission.

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Presented at the *Conference on Optimal Nutrition, Its Analysis and Application*, held at the George Williams College, Chicago, Ill., April 8-9, 1955.

Fortunately, this relationship has been true to a considerable degree, although recent evidence[1] indicates that certain types of nutritional deficiencies during the early developing period may produce injury of such a nature as to result in progressive degeneration as age advances.

Optimum nutrition might be described, then, as that which provides all dietary nutrients in respect to kind and amount, and in proper state of combination or balance so that the organism may always meet the varied exogenous and endogenous stresses of life, whether in health or disease, with a minimal demand or strain on the body's natural homeostatic mechanisms.

Several facts must be recognized when considering optimum nutrition. The first is that it is at present utterly beyond the reach of probably two-thirds of the world's population, whose main concern is still just getting enough calories. This fact presents one of the most acute and serious problems which our political leaders have to solve if we are to preserve the free world. On the other hand, optimum nutrition is well within the grasp of most of the people of this country with respect to the availability of appropriate foodstuffs. The nutritionist must, however, assume greater responsibility in the continued study of the problem and in the education of the public concerning the selection and use of its food supply. Further education is also required to point out the rational place and importance of nutritional supplements.

DIETARY REQUIREMENTS

Any attempt to understand the significance of optimum nutrition must take cognizance of the fact that certain dietary standards are already available for our guidance. These are the Minimum Daily Requirements of Specific Nutrients of the U. S. Food and Drug Administration, and the Recommended Daily Dietary Allowances of the Food and Nutrition Board of the National Research Council. The latter figures, arrived at after considered judgment based on the evaluation of the extensive nutritional literature, provide for a safety factor above the so called "minimum needs." The importance of these tables in providing "yardsticks" of good nutrition can hardly be emphasized enough.

On the other hand, recognition must be given to the important concept set forth by Williams[2] that individual biologic variation with regard to nutritional needs is so great in man that one may be led astray by the uncritical application of tables of dietary allowances for any one particular person's requirements.

The report of Pollack and Halpern[3] on the nutritional requirements of sick, wounded, and convalescent patients brings into focus another new and highly important concept—that of therapeutic nutrition. Here emphasis is placed upon the fact that disease is associated with a disturbed metabolism, which is often accompanied by large losses of vitamins, proteins, and other nutrients. It is further pointed out that convalescence from disease may be materially shortened and the patient more rapidly rehabilitated as an active, productive member of society if therapeutic amounts of nutrients are given. These levels suggested are generally considerably above those of the aforementioned Recommended Dietary Allowances.

From what has been said, it seems quite probable that a plane of nutrition exists which we may call "optimal nutrition," and which may or may not fall within the limits of the Recommended Dietary Allowances. It may prove quite difficult, however, to set down an arbitrary table of nutrient requirements which will provide "optimal nutrition" if it is understood that the individual's needs, under the kaleidescopic variety of the stresses of life, may be quite variable.

This merely serves to emphasize the importance of the Recommended Dietary Allowances as a reasonable guide to aid each individual in his particular circumstances to attain this goal of optimal nutrition.

It is easy to see why such great difficulty is encountered in trying to evaluate or describe clinically and objectively what is meant by optimal nutrition, when one considers that nutritionists and clinicians have considerable

difficulty in evaluating malnutrition itself. Much of this is due, as indicated before, to the fact that malnutrition produces gradual and insidious changes, which are often reflected as disease entities other than nutritional in character. Furthermore, nutritionists and clinicians have often been too concerned with the importance of signs and symptoms of the frank specific deficiency diseases before admitting a relation of the disease to malnutrition itself. It should be emphasized that every sick person, particularly a chronically sick one, has in his illness an important component of malnutrition, which has to be dealt with in relation to the disease for which he has made his appearance in the hospital, clinic, or physician's office.

STRESS AND HOMEOSTASIS

One of the intriguing facts about life is its truly amazing flexibility and capacity to adapt to unfavorable environmental circumstances. This fact has enabled man throughout history to survive untold hardship, starvation, and suffering in his never ending efforts to expand his horizons. The secret of man's success in conquering his environment lies in the ability of the body to maintain homeostasis. Claude Bernard first appreciated the importance of the "constancy of the milieu intérieur." Later, Walter B. Cannon arrived at the same concept concerning the body's ability to maintain the constancy of the internal environment. A similar, somewhat more sophisticated concept has been called by Selye[4] the *General Adaptation Syndrome*, characterized by three states: alarm, adaptation, and exhaustion, respectively. Selye has suggested that the increased secretory activity of the adrenal cortices during stress, or an imbalance in the secretion of the adrenal cortical hormones during stress, can produce certain diseases, such as hypertension and arteriosclerosis. These he calls diseases of adaptation.

It is important to note that nutrition plays an important role in determining the capacity of the body to adapt to stress and avoid the damage of the stage of exhaustion.

A somewhat less extreme point of view has been expressed by Ingle[5,6], who suggests that the increased secretory activity of the adrenals during stress serves to meet an increased need for the adrenal cortical hormones. Ingle further poses the idea[7] that the adrenal gland may play a "supporting or permissive role" in the adjustments to stressor agents, but does not often play a primary role in the etiology of disease.

It is clearly evident that various and complex adjustments in metabolic patterns enable man to function over a fairly wide range of environmental stress and still remain in the "zone of homeostasis" (Fig. 1). Under normal dietary circumstances, the range of blood glucose may vary, for example, between 80 and 120 mg per 100 ml. Yet, during starvation, blood glucose, which is so important for the metabolism of the central nervous system, is maintained at an adequate level by the process of gluconeogenesis. At the same time, fat metabolism is increased to meet the energy needs of the body with maximum conservation of the body proteins until the fat depots are brought to their irreducible minimum. In the diabetic patient we see such an exaggeration of this fat metabolism that ketone bodies accumulate in the blood and are swept out in the urine with the wastage of important sodium ions, hence causing a severe metabolic disturbance.

In the above example, then, we see that in the stress of starvation, homeostasis of blood glucose is maintained at the "level of normalcy" (Fig. 1). This can be done, however, only by paying the price of metabolizing body proteins or amino acids and by utilizing fat depots. This, of course, serves the useful function of preventing excessive drains on the absolutely essential protein stores of the body. Such, then, are the shifts of the body's economy in the face of any stress which tends to distort the level of normalcy. Again, all of these adjustments have a price, and if the stress is continued long enough, the zone of homeostasis is exceeded, and disease, which is but a manifestation of these changes, is the inevitable result. Stress then tends to alter the "milieu

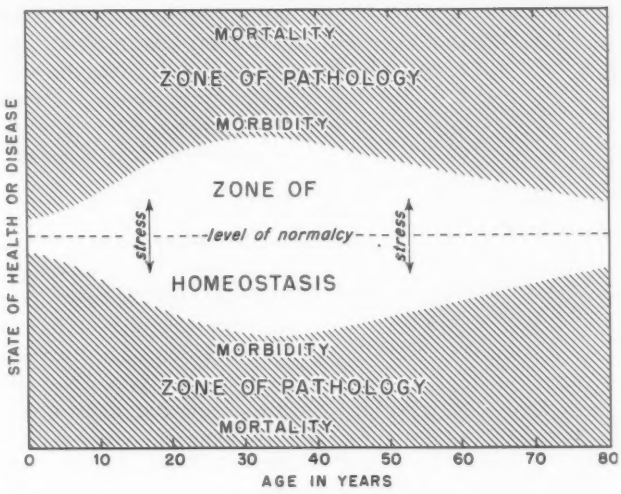

Figure 1

intérieur" away from the level of normalcy, while homeostatic mechanisms counter this action.

Further considerations (Fig. 1) make a bit more clear why nutritional aberrations are so slow in producing morbidity or mortality. A mild deficiency of a dietary essential might be continued for very long periods of time without exceeding the boundary of the zone of homeostasis. For example, a fairly normal blood level of vitamin C can be maintained on a low intake of the vitamin, but it has been shown that when a stress such as pregnancy occurs, the zone of homeostasis is rapidly exceeded and difficulties are encountered.[8]

Numerous experiments have shown conclusively that dietary factors may exert a profound influence on the level of intracellular enzymes. These specialized protoplasmic proteins spark the very metabolic machinery which makes homeostasis possible. The variation in enzyme levels in circulating fluids, such as the blood levels of acid or alkaline phosphatase, is so well recognized in man that these enzyme concentrations are used as valuable diagnostic aids in certain diseases. Of course, changes in the blood and tissue enzyme levels may be considerable before frank lesions can be seen. This again serves to emphasize that suboptimal or abnormal functioning of metabolic reactions do not necessarily bear a direct relationship to the signs and symptoms of disease that the patient may present.

It would seem desirable, however, to attempt to maintain the level of normalcy in the body tissues by exogeneous dietary means through optimal nutrition, so that when stress is encountered, the body's defense mechanisms need to be evoked as little and for as short a time as possible. In this connection, it should be pointed out that overnutrition, characterized primarily by caloric excess, may, and too often does, place just as grave a metabolic burden on the body and may lead to serious disorders and degenerative diseases.

It might be further pointed out (Fig. 1) that the zone of homeostasis and the mechanisms for maintaining the constancy of the internal environment are not the same throughout life. From a minimum in the newborn infant, the range of the protective homeostatic mechanism increases rapidly through childhood, reaches an optimum at early adulthood, and then gradually waxes and wanes with advancing age. This implies then that optimal nutrition may vary with the physiologic status

TABLE I

Basic Factors That Produce Disease States

I.	Congenital Malformations
II.	Infections (acute and chronic)
	1. Viruses
	2. Rickettsia
	3. Spirochetes
	4. Bacteria (and their toxins)
	5. Protozoa and Helminths
	6. Fungi
III.	Growths
	1. Benign
	2. Malignant
IV.	Physical Agents
	1. Light
	2. Heat
	3. Cold
	4. Radiation
V.	Chemical Agents
	1. Toxic or poisonous chemicals or drugs
VI.	Traumatic Accidents
VII.	Emotional Stress
	1. Psychiatric and neurologic disorders
VIII.	Metabolic and Endocrine Abnormalities
IX.	Nutritional Defects—The Deficiency Syndrome
	1. Calories
	2. Vitamins
	3. Minerals
	4. Proteins

at a given age during the life process. It further implies that the capacity of homeostasis may vary with each individual.

Further evidence of the adaptability that nature has provided is well illustrated by the fact that considerable pathologic change can occur in even the most vital organs without harm being grossly manifest. Considerable destruction of a large number of kidney nephrons may occur without disturbance in urine formation and electrolyte balance; extensive fibrosis and destruction of liver parenchyma can exist before gross signs of liver damage are seen; and many apparently normal people have markedly hypertrophied hearts, or are operating on one lung. It is only when stress of sufficient duration is applied that such abnormalities become evident.

Although the homeostatic mechanisms function remarkably well in preventing or minimizing disease states in man, circumstances do develop which produce disease. Any attempt to categorize the different disease-producing pathologic processes must, of course, recognize the fact that life is a continuum of correlated or interrelated activities and hence defines compartmentalization. The brief outline given in Table I is useful to indicate the range of events that can produce disease states.

PROTEIN NUTRITION

The importance of protein or essential amino acids in optimal amounts in the prevention of diseases will be especially emphasized, since protein occupies such a focal point in the constellation of nutrients which comprise the cell's protoplasm. Not only is the protein of the body the most abundant and constant protoplasmic component, with the exception of water, but derangements in the pattern of distribution of proteins in the cells leads quickly to pathologic changes. Protein is indeed the medium in which life itself revolves; and, as indicated before, it is the protein-active enzymes which make metabolism and life possible.

Although nutritional deficiencies *per se* exist as a separate and important category in the production of pathologic disorders, it is emphasized again that nutritional intakes at levels below the optimum may be important in the sequence of events over a long period of time that lead to injury induced by the other factors.

Pregnancy

Warkany's extensive observations with rats[9] make it clear that vitamin deficiencies early in gestation may lead to congenital malformation in the young. In relation to nutrition and pregnancy, it has been shown that maternal morbidity and fetal mortality decrease as the protein content of the diet is increased. Furthermore, a significant relationship was found to exist between the protein content of the diet and the serum protein concentration and hemoglobin content of the blood.[10] Burke and coworkers have also studied the protein level in the maternal diet as related to the pediatric rating of the newborn and found that "less than 75 grams of protein daily during the latter part of pregnancy results in an infant who will

tend to be short, light in weight, and most likely to receive a low pediatric rating in other respects."[11] Tompkins[12] has also pointed out the importance of adequate nutrition not only during pregnancy but prior to its onset. He finds that nutritional deficits in proteins and vitamins are a common occurrence among pregnant women.

Infection

From the important experiments of Cannon,[13] it has been shown that resistance to infection and the development of immunity depends on the supply of antibodies in the body. These substances in turn depend on the protein anabolic process and an adequate supply of protein of high quality. Increased metabolism and losses of nitrogen commonly occur in fevers associated with infections, and these losses can only be made up by increasing the exogenous protein supply. Complications of infectious diseases, particularly related to liver damage, may also require special attention with regard to protein nutrition.[14] Protein cannot be given haphazardly in conditions of severe liver damage, however. It has been reported[15] that some chronic alcoholic patients with very advanced cirrhosis of the liver and neurologic complications show an intolerance to protein when the dietary protein exceeds certain levels. This intolerance was shown by a characteristic "flapping" tremor which preceded coma. This serves to emphasize the importance of treating each individual case on its own merits.

Growth

The value and importance of adequate levels of high quality protein is well appreciated in all growth studies in every species examined. That growth does not mean a mere increase in size is indicated by the work of Allison,[16] who found that puppies fed wheat gluten increased their caloric intakes above those receiving whole egg protein. They became fat and soft, while those fed high quality protein became lean and hard, but both groups of dogs weighed about the same after 70 days on the respective diets.

Unfortunately, too little is known about why normal protein metabolism is diverted to the apparently "one-way street," which is seen in the growth of malignant tumors. Here body proteins are used in a frenzied, disorganized fashion to produce irreversible lesions. Again, however, this untoward growth is at the expense of the existing body tissues.

Malnutrition

The sequence of events in malnutrition as stated by Jolliffe is as follows.[17] Nutritional inadequacy results first in gradual tissue depletion (away from the level of normalcy), then to biochemical and functional changes, and finally to the development of anatomic lesions, which unfortunately represent only the most severe form of malnutrition. It is significant that most of the anatomic changes of severe malnutrition represent failures or inadequacies of protein anabolism. Perhaps the most striking example of protein malnutrition in the world today is that associated with kwashiorkor. Marked growth retardation, deficient muscular development, liver lesions, dermatitis, lesions of the mouth and gastrointestinal tract, and a reduction in the production of pancreatic and duodenal enzymes are seen in this disease.

Throughout the world the combination of low quantity and poor quality of protein intake is uniformly seen in areas where malnutrition is prevalent. Moreover, as the general standard of living and general health is improved, almost the first demand is for more and better quality protein.[18] Despite the cost of high quality proteins, the trend is toward an increased protein intake in the search for optimum nutrition.[19]

Trauma

Traumatic accidents, physical and chemical agents, all are capable of producing severe injury. In burns or in fractures of the long bones, for example, even in well-nourished people, tremendous quantities of protein are lost from the body, and it is only with the greatest difficulty that these losses can be compensated for by dietary means. It is

almost imperative, as shown by Artz,[20] to employ special protein supplements of high palatability for long periods of time to aid in the rehabilitation of patients with extreme burn damage.

It has also been shown[21] that protein deficiency is one of the important factors in the increased susceptibility to radiation damage. In radiation illness, prevention of infection, prevention of malnutrition, and attempts to correct the disorders in blood-forming systems are of paramount importance.

In the controlled trauma induced by surgical operations, especially in patients who have been ill for some time, nutrition may play an important role, especially in reducing the time for convalescence. Here again, careful studies[3] have indicated that "the postoperative physiologic status of patients fed excess protein was superior to that of controls."

SPECIAL PROBLEMS

Unfortunately, objective data concerning the relation of nutrition and emotional state are limited. This is indeed an important area for future study and development. From information that is gradually accumulating, it seems possible that at least one important factor in the production of obesity may be related to emotional insecurity and unhappiness. The idea that the fat man is a happy one is in need of serious re-evaluation.

The importance of carefully controlled nutrition is receiving increasing attention in the metabolic wards of our clinics and hospitals. Endocrine problems, such as diabetes mellitus, hyperthyroidism, and Addison's disease, and other metabolic problems, such as overweight, underweight, gout, diseases of the bones, liver, and blood, are all being considered in relation to the nutritional background and status of the patient. Dietitians are constantly being asked to prepare special and unusual diets for sodium restriction, peptic ulcers, tube feedings, *et cetera*. This indicates the importance of thoughtful collaboration between dietitian, biochemist, and physician in providing for the patient.

One factor that may induce abnormalities, not included in the above list, is that of "just getting old." Here the so-called degenerative diseases become of great significance.

Since the percentage of the aged in our population is increasing with the increase in the life expectancy, the problems of nutrition in geriatrics are of considerable importance. Stieglitz[22] has stated that "the elderly are prone to suffer from protein deficiency more than from any other form of deficiency." The common complaint of the aged—"a sense of habitual fatigue"—may reflect a mild protein deficiency. More extreme deficiencies may result in edema and atrophy of muscles or other tissues. Many old people, possibly because of the combination of loneliness, poor dentition, or just plain lack of interest and enthusiasm, are prone to prepare and eat easily prepared meals, high in carbohydrate, without ingesting an appropriate quantity of higher quality protein available in meat, eggs, and milk. It has been observed[23] that many elderly patients benefit by diets providing two grams of protein per kilogram of body weight daily. The mechanical difficulties of eating this much protein, however, often pose a real problem for the aged.

SUMMARY

Optimal nutrition has been visualized as that which maintains a level of metabolic normalcy so that when the organism is exposed to stress, the normal protective homeostatic mechanisms can be put into operation rapidly, with a minimum of strain, and for as short a time as possible. Because of this zone of homeostasis, it is difficult to establish the quantities of nutrients which provide optimal nutrition. These may vary considerably, depending upon individual biologic variability, sex, age, and both exogenous and endogenous stress.

The attainment of optimal nutrition poses a real challenge to the nutritionist, but is within the range of a population educated to the proper use of an abundant and varied food supply.

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Some Recent Developments in Oral Feedings for Optimal Nutrition in Burns

By CURTIS P. ARTZ, M.D.* HARRY S. SOROFF, M.D.† ELINOR PEARSON‡ AND ROBERT P. HUMMEL M.D.§

THE NUMBER of survivors after severe thermal injury has increased in recent years because of more physiologic resuscitative measures, improved surgical techniques, and better control of infection. This increase in the number of survivors has re-emphasized the problems of convalescence. In some burn patients this period may last for several months, resulting in as much of a physiologic drain on the patient as the acute burn. Convalescence can be greatly shortened by increased attention to optimal nutrition.

Injury is followed by a period of negative nitrogen balance. This period of catabolism lasts for varying periods of time, depending upon the severity of the injury, the state of wound healing, and the nitrogen and caloric intake.

This presentation is concerned principally with the magnitude of protein losses, optimal levels of nutritional intake, and the achievement of optimal nutrition by oral supplemental protein feedings.

MAGNITUDE OF PROTEIN LOSSES

In an attempt to ascertain the magnitude of losses of a burned patient, complete metabolic balance studies were carried out on eight severely burned patients who were in a good nutritional state prior to their injury.[1] They had an average total burn of 40 per cent, 19 per cent of which was third degree. All of the patients in this group survived the study period. For the eight patients, the duration of negative nitrogen balance or the catabolic phase averaged 33 days.

The patients had an average daily intake of 95 grams of protein (15.2 grams of nitrogen) and 3000 calories. Throughout this period, these patients received a palatable, measured diet with an *ad libitum* intake. They were encouraged to take high protein feedings between meals and received the maximum intake of protein achievable without forced feeding through an intragastric tube. During the first week after injury, they could tolerate very little oral intake, but during the latter part of the study period the daily intake approached 200 grams of protein and 5000 calories.

During the 33 days of the catabolic phase, the daily nitrogen loss averaged 26.5 g, or 166 g of protein. The daily negative nitrogen balance averaged 10.4 g or 65 g of protein. The total losses for the catabolic period were most extensive. The total nitrogen loss per patient averaged 842 g. The weight loss in each patient averaged 29.5 g (13.4 kg) or almost one pound per day. This loss of 13.4 kg represented 917 kg of lean body mass and 3.7 kg of fat.

In spite of these extensive losses, wound healing did not seem to be impaired and skin grafts took well during the catabolic period. On the other hand, it is well known that burned patients who remain in negative nitrogen balance for prolonged periods of two months or more become depleted and fall into a state where the take of skin grafts and wound healing is impaired.

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Presented at the *Conference on Optimal Nutrition, Its Analysis and Application*, held at the George Williams College, Chicago, Ill., April 8–9, 1955.

OPTIMUM LEVELS OF NUTRITIONAL INTAKE IN BURNS

The optimal vitamin therapy after thermal injury has never been determined. On an empirical basis, it is common practice to administer several times the recommended normal daily requirements to patients in a condition of stress. In most instances, large amounts of all the known vitamins are probably not indicated.

Supplemental vitamin therapy is recommended for severely burned patients, but there does not appear to be any evidence to suggest that unusually large quantities of all vitamins are required. At least one or two grams of vitamin C should be given daily. In addition, the following daily doses are recommended: Thiamine hydrochloride 10 mg, riboflavin 10 mg, niacin amide 100 mg, pyridoxine hydrochloride 2 mg, calcium pantothenate 20 mg, folic acid 1.5 mg, and vitamin B_{12} 4 μg.[2]

During the days immediately following thermal injury, vitamins should be given by the parenteral route; later, oral intake is preferred. Two standard therapeutic vitamin tablets are sufficient, in addition to one or two grams of vitamin C.

The aims in protein therapy after thermal injury are (1) minimization of nitrogen depletion as soon as possible after injury, and (2) repletion of nitrogen during later convalescence. There has been abundant clinical evidence to show that the significantly burned patient requires about two to three grams of protein per kilogram of body weight and a total daily caloric intake of approximately 30 calories per gram of protein. This means that most burned patients should receive between 150 and 200 grams of protein, and between 4000 and 6000 calories daily, depending upon the extent of depletion and the severity of the injury.

The protein used should be of high biologic value; therefore, it should be either animal protein, or vegetable protein properly supplemented with animal protein. Whole natural foods are preferred to synthetic protein. When indicated, additional calories may be obtained by the use of a palatable fat emulsion. During the use of any high protein, high caloric formula, sufficient water must be supplied to insure adequate excretion of nitrogenous end products and excessive electrolytes.[3]

ACHIEVEMENT OF OPTIMAL NUTRITION BY ORAL SUPPLEMENTAL PROTEIN FEEDINGS

After severe thermal injury, the convalescent period extends over several weeks or even months (Figs. 1a, b, c, d, and e). Immediately after injury, an adequate intake cannot be expected because the patient is usually not able to take a full hospital tray. During this period, nitrogen depletion can be minimized by encouraging the patient to take a high protein liquid mixture. As his condition improves, he will probably consume more food from his hospital tray and, therefore, approach an optimum intake. However, he soon tires of hospital food. In spite of the most appetizing menus prepared by the best diet kitchens, burned patients rarely take an adequate amount of protein from the hospital tray for very long periods. The best method for minimizing protein depletion seems to be by the use of an acceptable high protein, between-meal liquid feeding. If such a mixture is palatable, patients will take it for prolonged periods of convalescence.

Large amounts of proteins can be given by intragastric nasal tube feedings. A small plastic tube can be inserted into the stomach and large quantities of proteins and calories can be given by this route. However, tubes are uncomfortable and unless there is evidence of impending severe depletion tube feedings are unnecessary. They should never be used in the immediate post-burn period because of the reflex gastrointestinal ileus that occurs during the first few days after an extensive burn. Likewise, they should never be used when the reflexes are depressed or when there is danger of aspiration.

If an adequate amount of supplemental protein can be given, tube feedings are usually unnecessary except in very extensively burned patients or patients that may become depleted. However, when it is obvious that an adequate nutritional intake is not being

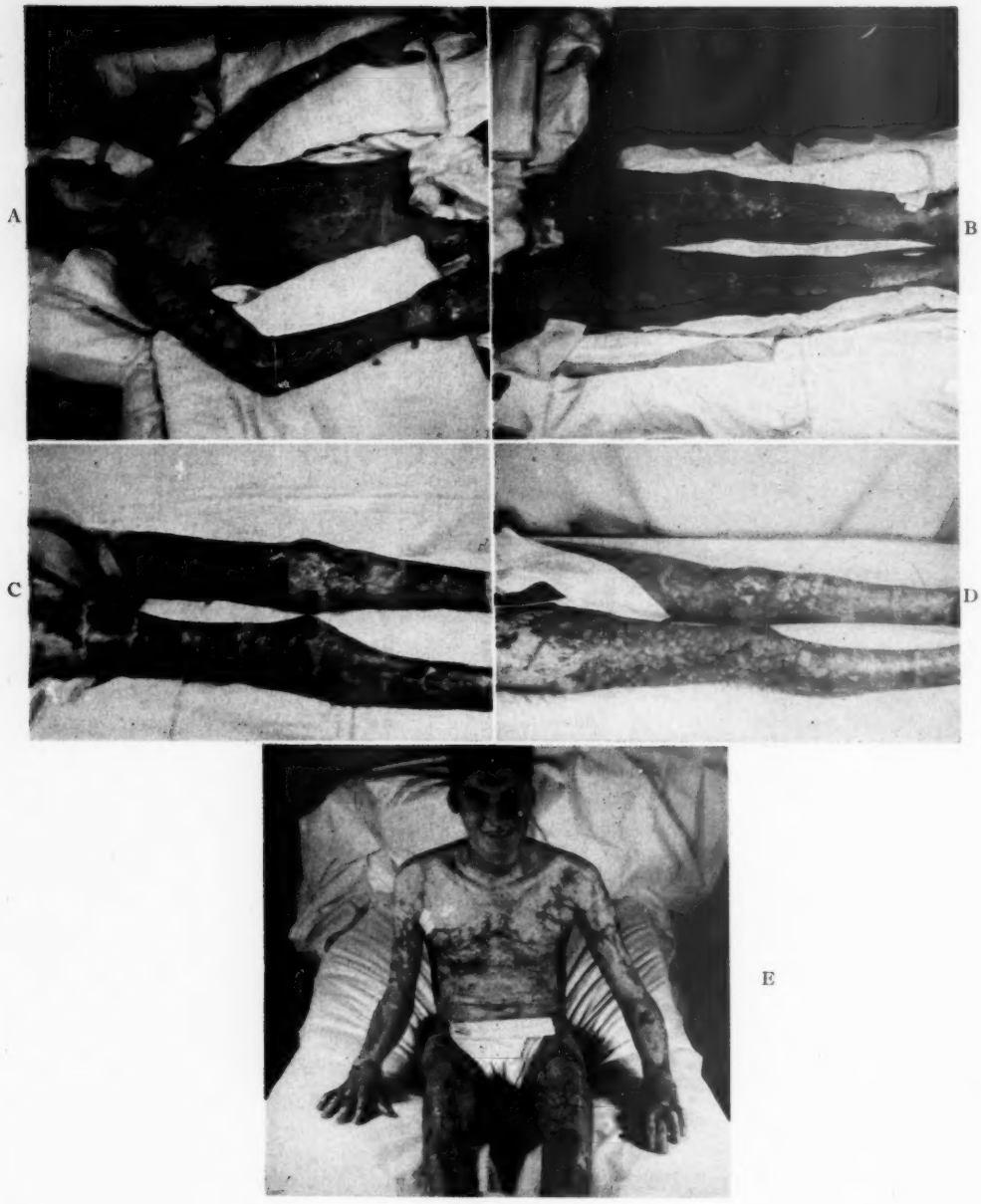

Figure 1

Fig. 1. A. This soldier sustained a 70 per cent burn, 43 per cent of which was third degree, when a shell exploded in a howitzer chamber. This photograph was taken 11 days after injury. There is partial healing of the face and a good protective crust has formed over the chest and arms. B. Eleven days after injury. There are deep circumferential burns of both legs and buttocks. C. Forty-eight days postburn. After removal of the deep eschar, the patient did not have an adequate amount of skin for covering the burn wound. Homografts from a recently deceased body were applied, and this photograph was taken after homografts had been in place 28 days. The homografts disappeared about 47 days after application. By that time the patient's general condition had improved and postage-stamp grafts taken under local anesthesia were applied. D. This photograph shows the patient at the time of discharge from the hospital when the wounds had healed. He was in a good nutritional state. Although he lost 50 pounds, he regained 30 pounds following the use of tube feedings and high protein between-meal supplemental feedings. E. Complete healing of the legs after the application of postage-stamp grafts.

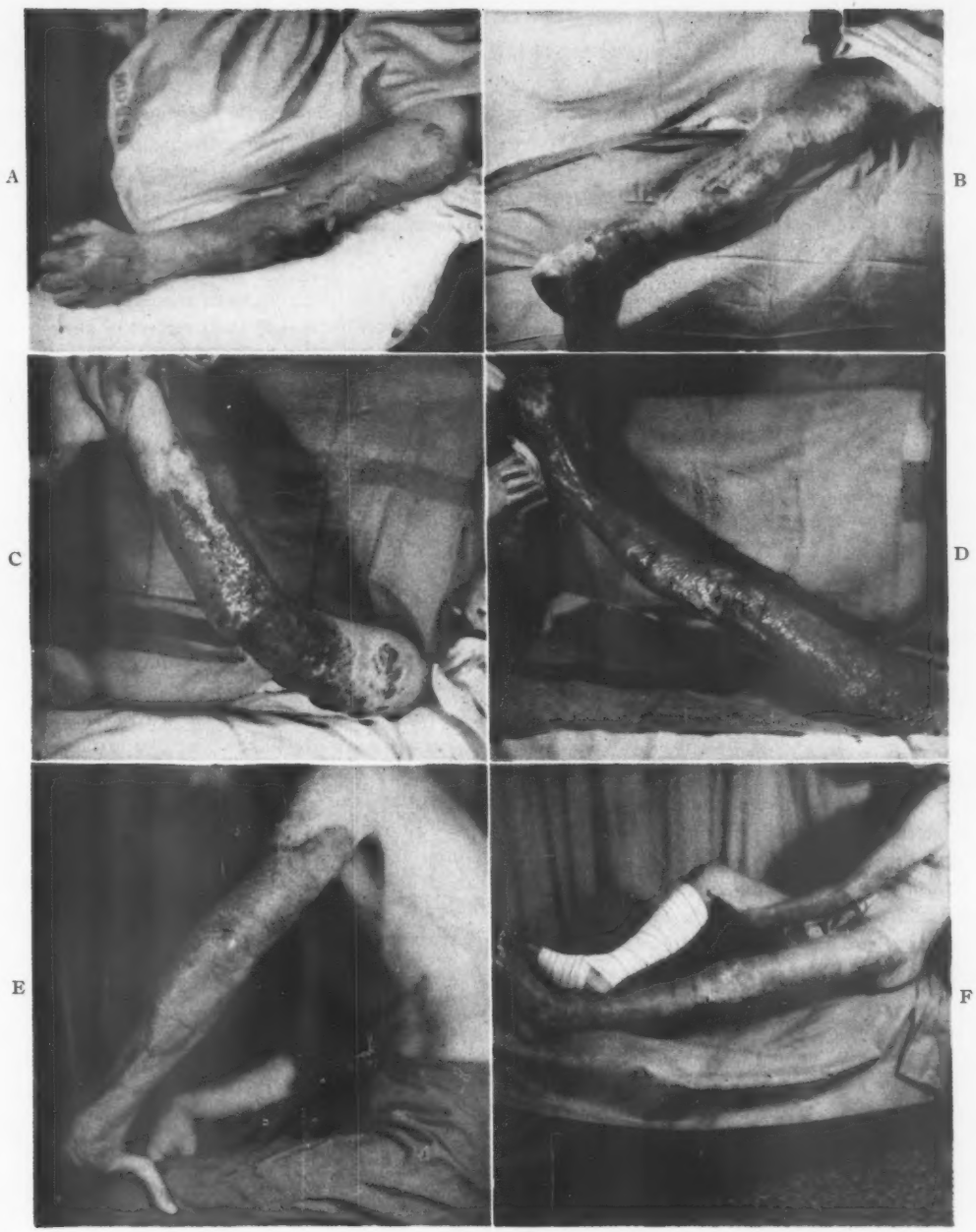

Figure 2

Fig. 2. A. This pilot sustained a 27 per cent burn, 22 per cent of which was third degree, in an aircraft accident. This photograph shows second degree and third degree burn of the arm immediately after the injury. B. Deep second degree and third degree burns of the leg immediately after injury. C. Twenty-seven days postburn. The area is ready for grafting. The patient had received 1200 cc of high protein supplemental feeding daily. D. Twenty-seven days postburn. The leg is ready for grafting. The patient had lost approximately 15 pounds of weight. E. Eighty-three days postburn. The arm is completely healed and the patient weighs only five pounds less than his preburn weight. F. The left leg is completely healed and the patient is ready for discharge. The elastic bandage on the right leg is for support of a healed fracture of the tarsal bone. In spite of very extensive injuries this patient remained in a good state of nutrition throughout his entire hospital course. Complete healing of this extensive wound was accomplished in less than three months. Optimal nutrition was provided by large quantities of a palatable high protein supplemental feeding, which the patient consumed throughout his entire convalescence.

achieved and the patient is steadily becoming depleted, there is no substitute for tube feedings.

If special attention is paid to nutritional therapy as soon as the patient is admitted, a program can be outlined whereby an adequate intake will be maintained. It should be explained to the patient that the high protein, between-meal supplement is required for optimal convalescence. If this supplement is palatable and served to the patient three or four times a day, depletion will be minimized during the first few weeks after injury and later this added protein supplement will provide the necessary requirements for repletion of protein stores.

The desirable protein supplement should provide primarily proteins without a large number of calories. Increasing the caloric value of supplements frequently reduces the patient's appetite. In addition, when large quantities of carbohydrates and fats are used the supplement is not as palatable. Supplemental calories are usually provided by the intake from the hospital tray.

In the treatment of more than 600 burned patients hospitalized during the past four years, Provimalt* has been used extensively as an in-between-meal supplemental protein feeding and it has proved most efficacious (Figs. 2a, b, c, d, e, and f). Twenty-four grams (4 level tablespoons) of Provimalt powder are mixed with 227 ml of whole milk and flavored with 20 g of chocolate syrup. The resultant mixture (total volume 250 ml) contains the following: calories 296, protein 21.7 g, carbohydrate 28.6 g, and fat 9.3 g. When it is freshly prepared and served cold, patients find it very palatable and take it for many months. They may consume from 750 to 2000 cc of this mixture a day. Its chief advantage seems to be its palatability. Patients rarely tire of it and usually continue to take it throughout their entire convalescence.

* Provimalt is a high protein supplement powder supplied through the courtesy of Blake Snyder of Humanic Brands, Summit, N. J.

SUMMARY

Improved techniques in the management of burns have increased the number of survivors, which in turn has re-emphasized the problems of convalescence. Convalescence may be shortened by optimal nutrition.

Protein losses after burns are quite extensive. In eight patients on metabolic study, the average daily protein loss for the 33 days of the catabolic period was 166 grams. Although the patients were in negative nitrogen balance during this period, they were not severely depleted and wounds healed well.

The problem of nutrition in the severely burned patients seems to be prevention of protein depletion. Some type of high protein supplemental feedings is required because the patient is usually unable to take an adequate amount of protein from the hospital tray.

During the past four years Provimalt, a palatable high protein supplement, has been found to be most efficacious in the treatment of more than 600 burned patients. Its chief advantage is that patients accept it over the entire course of prolonged convalescence.

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The Diagnosis of Malnutrition in Well-Nourished Communities

By A. M. THOMSON B.SC., M.B. CH.B., D.P.H.*

JUST AS the provision of clean water wiped out cholera and typhoid fever, so nutritional improvements have practically eliminated the major deficiency diseases from most Western communities.

The city of Glasgow helped to pioneer the industrial expansion of the 19th century, and became one of the places "where wealth accumulates and men decay." Many of its inhabitants lived in degradation, crowded together in tenement slums. Few of the slum children, after weaning from their mother's breasts, ever drank milk except in the smallest quantities. Smoke from the factories and foundries obscured the rather small quota of sunshine which favors western Scotland. An observer said that "during the seventies (of last century) the surgeons began to perform the operation of osteotomy to counteract the injurious effects of rickets on bones. . .operations for contracted pelvis in childbed have increased in recent years".[1] Things began to improve slowly after the turn of the century, but Munro Kerr[2] wrote in 1916 that "Taking the cases in the Glasgow Maternity Hospital for the last ten years, decided pelvic deformity has been found in fully 30 per cent of indoor patients. This high proportion is to be accounted for by the prevalence of rickets in this city." Just after the industrial depression of 1930–32, rickets was still a familiar disease in the wards of the children's hospital. The students of today consider themselves lucky if they see a case at all.

The recent disappearance of major deficiency diseases has been noted in the United States also. I have been shown a letter from the late Dr. V. P. Sydenstricker, of the Medical College of Georgia, saying almost wistfully that he could no longer find cases of pellagra to show to students. This was about 1946.

To the extent that the long struggle against deficiency disease is virtually over, our communities can be considered well nourished. But studies of growth and of vital statistics, as well as clinical observation, suggest that there is a wide "twilight zone" between mere absence of deficiency disease and the highest level of health that can be achieved through diet. Our present concern is with the diagnosis of malnutrition within this zone.

NUTRITION IN RELATION TO GROWTH, HEALTH, AND MORTALITY

It will, I think, be generally agreed that improving growth is good evidence of improving nutrition.

During the past 40 years, the average height of Glasgow schoolboys has increased about 3 inches (7.5 cm) and the average weight about 9 lb (4 kg).[3] There has been much argument as to whether adult stature has also increased; Boyne and Leitch[4] have shown that, although the available British data are not adequate to settle the point, Scandinavian data "give clear evidence of improving stature in a population similar to our own." Americans also are growing taller,[5] and a British newspaper (*Manchester Guardian*, October 28, 1954) noted recently that the Fifth Avenue Association in

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New York has asked for shop awnings to be at least seven feet above the sidewalk instead of the present minimum of six feet; that the average G.I. in the Second World War was six-tenths of an inch taller and 9 pounds heavier than his predecessor in World War I; and that "king-size" beds, $82^1/_2$ inches long, have come on the market. The newspaper added that "The American trend to tallness is explained by scientists as being mainly due to adequate nutrition allowing the American child to attain the maximum stature of which he is capable." It would be interesting to know if this "trend to tallness" has occurred in the groups who, twenty years ago, would have been considered well nourished. Before the war we[6] found that children given extra food designed to eliminate the major defects in the family diet "at all ages and in all (food) expenditure groups gained (in height) more than controls, and there is no clear evidence that the increment was less as food expenditure rose."

Better growth has been accompanied by a most remarkable improvement in mortality statistics, reflecting a change in general health which is difficult to illustrate statistically, but which I believe to have been obvious and unquestionable. The Chief Medical Officer of the Ministry of Health in England commented in 1946 that: ". . .the child at the end of this war was bigger, more resistant to disease, better nourished and in every way had borne the strain of wartime better than his predecessor of the last war, . . ."[7]

So many influences have contributed to improvements of health during the past few decades that it is not easy to show the special importance of nutrition. Experience during the war years was therefore especially valuable. In Britain, accelerated growth in children[3] and an unprecedented fall in such vital statistics as the stillbirth and neonatal death rates[8] occurred at a time when, although morale was high, civilians lived under conditions of great stress and strain. Houses were destroyed or damaged in great numbers and new building practically ceased. The "blackout" made living and working conditions after nightfall unpleasant and unhygienic. Everyone who could work, even the women, had to work in industry or in the forces. Transport was scarce and grossly overcrowded. Family life was often strained by the absence of the breadwinner, by the evacuation of women and children from the great cities to safer areas, and by the working and living conditions already mentioned. The medical and social services were more concerned to meet urgent and often unfamiliar new needs than to make planned general progress.[9] The one great exception was the national food administration which—inspired by such pioneers as John Boyd Orr, and fortified by the preliminary data of the prewar Carnegie Survey[6]—began, early in the war, a carefully planned drive toward better nutrition, particularly of mothers and children. The drive took place in the context of full employment and rising wages, and was supported by nation-wide propaganda, controls and rationing, and by such measures as improving the nutritive value of bread. And it was made possible, *inter alia*, by the generosity of the American people and Lend-Lease. We in Britain had, in fact, a deliberate feeding experiment on a grand scale, conducted at a time when few other social advances could be made. I doubt if even the more starry-eyed nutritionists of the 1930's would have dared to predict the whole extent to which the experiment succeeded in the midst of wartime difficulties and restrictions.

It is extremely interesting to find that reductions of mortality were achieved as notably among the best-fed prewar groups in Britain as among the worse-fed. Accelerations in the rate of fall of stillbirth and neonatal death rates during the war years occurred in many countries, including the United States, and nutritional improvements associated with rising economic standards may be presumed to have been a major cause. The hypothesis of nutritional improvement even seems capable of extension—at least in part—to such unlikely situations as that of Holland during the war. Up to 1940, the Dutch stillbirth rate was, at 25 per 1000 births, the lowest and most stable national rate in the world, and it might reasonably have been assumed that the prospects of further

reduction were remote. Yet Holland was occupied by the German army in 1940, and the stillbirth rate fell to 21 in 1941 and 19 in 1942. Analysis has shown that the main fall was in stillbirths attributed to toxemia of pregnancy—a condition widely believed to respond favorably to restriction of diet during pregnancy.[8] There was no dramatic change in the birth rate at the time, nor was there any advance in the medical treatment of toxemia.

It is difficult to peer into the future, but this brief history suggests that although we have come a long way since the days when deficiency disease was commonplace, we still have a considerable distance to go. We have no reason to think that any large community, or any large section of a community, has yet attained the nutritional ideal. It may take several generations of optimal diet before the final effects are realized.

DIETARY STANDARDS IN THEORY AND PRACTICE

Orr[10] defined an optimal diet as one "which will keep people in health; and the standard of health adopted is a state of well-being such that no improvement could be effected by a change in the diet." I would hesitate to define in detail the clinical characteristics of this nutritionally ideal state of health, or to assert that it has been attained even by our best-fed groups. We can obtain the best available approximation to the ideal from the clinical characteristics of our most healthy citizens; and by recording the diets that such people eat we can specify the diets which support this kind of health. Certainly we are not yet in a position to construct an optimal diet on physiologic principles; as the National Research Council[11] has said: "the optimum intake of essential dietary constituents remains largely speculative."

I have discussed elsewhere[6] the virtues of dietary targets based on the observed food habits of our healthiest citizens. Dietary standards obtained in this way are practical, because they are related to known levels of health. Groups using diets below the standards are not *necessarily* malnourished, but if they show evidence of impaired growth or relatively high rates of morbidity and mortality, it is at least safe to assume that these might be improved by a different diet. It is sufficient for this assumption to know that in both our countries large sections of the population are less healthy *and* less well fed than other sections. For some of these, immediate nutritional targets may require modification. The F. A. O.[12] recommendations on calorie requirements distinguish between the current ideal and the immediately practical. It is proposed that all children should receive the standard allowances, whatever their size; but allowances for adults should be adjusted in accordance with body size. If the next generation of adults should be larger, in consequence of improved nutrition, their calorie allowances will be automatically upgraded. And the calorie needs of "reference" adults and children will, presumably, be adjusted if future research shows this to be necessary in the interests of health and efficiency.

THE ASSESSMENT OF HEALTH

I have tried to stress that the goal of nutrition policies should be optimal health, and do not apologize for emphasizing the obvious, because it would sometimes appear that our target is a pattern of scientifically approved eating habits or of blood chemistry. *Since optimal nutrition cannot be defined without reference to health, we must be in a position to measure health.*

In assessing our progress during the past few decades I have dwelt on measures of growth and of body size, and on vital statistics. The fact is, that when deficiency diseases disappear, we have no other clinical criteria by means of which exact and objective comparisons can be made between the nutritional status of two populations, or of the same population at different periods of time.

In general, the competent clinician can express a useful opinion as to whether a given person has been well or ill fed or is responding favorably or otherwise to a change of diet, but this opinion is based on indications which are difficult and usually impossible to record consistently enough to yield reliable statistics. The abnormal merges imperceptibly into the

normal; the clinician, asked for an opinion as to nutritional status, has to describe "shades of gray"—and "grays" of varying tone at that—and it is scarcely reasonable to expect observations which are highly subjective to be reducible to reliable black and white statistics. Bean[13] has made the pertinent comment that such data "acquire the aura of accuracy when tabulated and dealt with mathematically. . . No conclusions can be more valid than the data upon which they are based." The data of Babcock *et al.*,[14] derived from a different American population, seem to support Bean's views. Working with children in prewar Britain, we found that signs and symptoms recorded with the greatest care by two specially trained physicians working together failed to differentiate successfully groups subsisting at different nutritional levels; or if they did, they failed to demonstrate the effects of supplementary feeding.[6] These children were almost certainly less well nourished than the average American child of today, and I have no doubt in my mind that some of them were quite severely malnourished. Even in India, I found[15] that the progress toward health of malnourished Indian recruits, derived from populations in which deficiency disease was fairly common, could not be delineated successfully by trends in the incidence of so-called specific criteria of nutritional deficiency. By contrast, in both the Carnegie and the Indian feeding experiments, definite and unmistakable effects on growth were readily demonstrated. The failure of the clinical signs to respond in an obvious way contrasted sharply with the ready cure of true deficiency disease by specific therapy.[16]

In my opinion, we have been misled for years by attempts to make serviceable statistics out of material which is inherently unsuited to this treatment, as well as by the notion that the twilight zone between deficiency disease and optimum health is characterized by signs and symptoms referable to one specific deficiency or another. I have reviewed this topic elsewhere[17] and have come to the conclusion that the clinical features of the "twilight zone" are, in general, to be regarded as nonspecific, i.e., they can be produced by many different deficiencies or even by underfeeding. In addition, they may have nondietary causes.

Such considerations mean that clinical judgments are of limited value for the assessment of minor dietary defects, and that they are almost useless for purposes of epidemiologic demonstration. This does not mean that they are unimportant and can be neglected. The clinical characteristics of the twilight zone are obvious enough to the discerning eye. In the field in which I am now working—that of human maternity—we observe that the typical ill-nourished mother from the slums is rather small and often ill-proportioned, and may have poorly developed muscles. Her skin lacks the "bloom" of good health and her gums and teeth are usually notably unhealthy. Her movements lack springiness, and her manner vivacity. She seems to age rapidly compared to a mother living in healthier circumstances. Her person has a "second-hand" appearance—an indefinable but noticeable aura of shoddiness—which may match the impression given by her clothes.

We erected the hypothesis that mothers in this clinical condition were physically stunted and physiologically inefficient and that poor diet was an important causal factor. On her first attendance at the antenatal clinic, each pregnant woman is placed in one of five grades of general health, ranging from "very good" to "very poor." The first finding was that the poorer the general health, the smaller the stature; and, indeed, height has proved to be an extremely useful measure for differentiating adults into groups with different nutritional and health characteristics. It has the supreme merit of being wholly objective.[18,19]

As regards stunting, Bernard[20] found by means of x-ray pelvimetry that minor but clinically important degrees of contraction at the pelvic brim occur commonly in small women, especially when in poor general health, but rarely in tall women, especially when in good general health. Incidentally, Bernard's study showed clearly that the so-called "android" pelvic brim supposed to be characteristic of the male is to be found equally commonly

in ill-grown females and ill-grown males, and that the "gynecoid" pelvic brim is as characteristic of the well-grown male as of the well-grown female.

As regards physiologic efficiency, we have found that tall women and women graded antenatally as being in "good" or "very good" general health have lower prematurity and still-birth rates than small women or those in worse health.[19] The incidence of difficult labor also increases, other things being equal, as maternal height becomes less.[21,22] Under the conditions of our investigations, the conclusion seemed inescapable that most short women were not genetically small, but had been made so by the conditions experienced during growth. We are, of course, unable to undertake diet surveys retrospectively, but this conclusion is supported by the distribution of height by social class[23,23a] and there is no doubt that small and unhealthy women tend to take worse diets during pregnancy than tall and healthy women (unpublished data). Such findings do not necessarily prove that nutrition is important; correlation is not causation. Poorly fed women usually live in generally poor circumstances, many aspects of which may impair growth and reproductive efficiency. We can eliminate some of the conflicting factors by appropriate methods of analysis. For example, we have been able to satisfy ourselves, by using the "matched pairs" technique, that women doing paid work until a late stage in pregnancy are no more likely to experience prematurity than those who stop work early.[24] The ultimate proof of the importance of nutrition must come from an adequately controlled feeding experiment or experiment in diet education. As already indicated, I hold that wartime experience in Britain provided an uncontrolled but none the less convincing demonstration of what improved feeding can do. *Ad hoc* feeding experiments on pregnant women have so far been much less satisfactory as evidence and, indeed, the technique is far from easy.

It is always tempting to discourse at length upon one's current work, but I must return to the main theme. The use of body measurements in the diagnosis of malnutrition is not, of course, wholly free from snags. I do not know of any argument against the hypothesis that accelerated linear growth, not attributable to an endocrine abnormality, is beneficial to health. But the same cannot be said of growth in weight, at least in respect to adults. Fat adults tend to be unhealthy, and we now think that weight should not increase after the age of about 25 years.[11] In general, the complex indices based on combinations of weight, length, and/or circumference seem to have fallen out of fashion; this is no doubt because many such indices in the past were derived quite arbitrarily from any set of measurements available at the time, and with little or no reference to biologic principles. We may obtain more useful and sensitive indices if we study the orderly sequence of changes in body proportions during growth, and the effects of nutritional differences upon the shape attained in adult life. Leitch[25] has given an illuminating discourse on this topic.

Vital statistics can be used with great profit in assessing standards of health, but must be interpreted with care, since they are subject to many non-nutritional influences. Mortality rates in fetal and neonatal life are of special interest from the nutritional point of view because they are not greatly influenced by infection, nor by the degenerative conditions which are becoming so important as causes of adult mortality, especially after middle age. Pregnancy is a test of the physiologic efficiency of the organism at its prime, and it is reasonable to suppose that, other things being equal, the well-nourished and healthy mother will be best fitted to produce a well-grown baby of high vitality. With good clinical records, one can eliminate many deaths clearly due to non-nutritional causes, though even here it is necessary to be cautious. A well-nourished and vital baby may withstand a degree of anoxia or trauma which suffices to kill one less well-endowed. A baby who died after forceps delivery was found to have suffered cerebral damage. The obstetricians were greatly concerned about the technique of the delivery. But the most interesting point, that the baby weighed only $2^1/_2$ lb and would probably have

died anyway, was not given much attention. Why was the baby premature? Was maternal nutrition at fault?

In speaking of "maternal nutrition" it should be noted that I do not mean nutrition during pregnancy only. The mother is the product of a lifetime (or more) of nutritional experience. If, to take a crude example, she has a contracted pelvis due to malnutrition in childhood, no amount of good feeding during pregnancy can remove the defect. There may well be other, more subtle, but equally permanent disabilities.

My experience of biochemical aids to the diagnosis of malnutrition is limited, and I have little to say about them. The great difficulty at the moment seems to be that no biochemical measurement has been convincingly related to differing levels of health, at least above the level of obvious pathology. To know that group A has more of a given substance in its blood than group B is not, by itself, evidence that group A is the healthier.

VARIATIONS AND LIMITATIONS

There is no such thing as "*the* ideal diet," but a series of optima depending upon the population concerned, the environment in which it lives, and the particular aspects of health judged to be most valuable. We already recognize this by varying calorie allowances in accordance with body size, activity, environmental temperature, and so on. There are other ways of varying diets so as to obtain the highest possible levels of health and efficiency in specific circumstances. Wartime experience and investigation demonstrated the importance of providing ample fluid for men working hard in tropical conditions, and of replacing salt lost in the sweat. More subtle examples than these may be provided by future research. The common preference of athletes for diets containing large quantities of meat may be simply a curiosity of behavior, but the possibility cannot be dismissed that a physiologic benefit is obtained.[26]

Although it is no doubt generally true that persons judged to be in good health in one or more respects are healthy in other respects also, health is not indivisible. The average Indian villager is clinically malnourished but has excellent teeth as a rule; our general health is much better, but few of us can boast of perfect teeth in adult life. The diet which impairs our dental health promotes our general health, and conversely for the Indian. It does not, of course, follow that we have inevitably to choose between good general health and good teeth; but I have never seen the specification of an "optimal" diet acceptable to Westerners in general which will ensure both. The preliminary findings in a current investigation in Aberdeen suggest that in selecting an "ideal" weight gain during pregnancy—a matter which is closely related to the energy value of diet—it may not be simple, by manipulation of weight gains, to achieve the lowest incidence of pre-eclampsia and of prematurity (birth weight $5^1/_2$ lb or less) simultaneously.

Our problem is therefore complex. We need to understand much more about the nature of malnutrition which, in the present context, I take to be a restriction of physiologic potential by imperfect diet, rather than a disease or group of diseases. One of the chief characteristics of any human population, even of one race, is the great variability of the individuals who make it up. The "physiologic matrix" is very different from that of a highly inbred population of laboratory animals carefully reared under standard conditions. What degree of variability can be regarded as physiologic rather than pathologic? What is the physiologic basis of differences of growth and vitality? Can differences of growth exist without differences of vitality? How are such differences related to nutrition? What is the physiologic potential, how far are we from it, and what prevents its attainment?

It is almost certainly unreasonable to expect that, when we are in a position to specify and apply generally an optimal diet of any kind, no one will show any of the clinical signs of imperfect nutrition; any more than that on an "ideal" calorie intake no one would become too fat or too thin.

There is no doubt whatever that clinical signs characteristic of dietary deficiencies can

occur in some people taking a good diet and in the absence of any obvious nondietary cause. Physicians are familiar with the occasional case of mild hypochromic anemia, clinically indistinguishable from the iron-deficiency state, occurring in the absence of any history of blood loss or toxic factor or obvious dietary inadequacy, which responds poorly, if at all, to any form of oral therapy.

Fifteen years ago I was studying dark adaptation in relation to vitamin A intake.[27] Fifty-three colleagues at the Rowett Research Institute were used as controls; all were in normal good health and were taking a good diet, supplemented for a week prior to test with 17,000 IU vitamin A daily in the form of halibut liver oil. The time taken by these subjects to adapt to dark completely, as measured by a carefully standardized technique, varied from 7 to 25 minutes. Two other apparently healthy colleagues were found to be suffering from a clinical degree of night-blindness. One of these took halibut liver oil for months without effect; regular observation was discontinued, but on retesting casually some time later he was found, unaccountably, to give perfectly normal results. The other responded slowly and incompletely to vitamin A concentrates in very large doses given by mouth, and then became completely normal a few hours after an intramuscular injection of 100,000 IU vitamin A. In India, I noted[16] that "in a minority of afebrile individuals the characteristic lesions (of riboflavin deficiency) may persist even when the diet is quite adequate. In such cases a defect of absorption or metabolism probably exists. As a rule, however, a (good). . .diet will clear up all major signs within 3 to 6 months. The process is accelerated by giving milk."

Such experiences are not very rare in clinical nutritional investigation, and emphasize that individuals vary in their response to diet as well as to nutrients given therapeutically. In the absence of disease, it is possible that the question is one of varying limits of physiologic adaptation.

Some individuals cannot adapt fully to a normal diet. Celiac disease is a crude example. Another is the inability to break down a specific amino acid or one of its normal derivatives, so that the individuals concerned go through life as phenylketonurics, alcaptonurics, and so on, depending on the nature of the metabolic defect. Rimington's[28] account of some of these strange anomalies also indicates how alternative pathways of metabolism may be used, and doubtless some pathways are more efficient, physiologically, than others. In the same way, some individuals may have a greater capacity than others to adapt efficiently to an optimal diet. It seems very likely that considerable physiologic variability will remain even when all restrictions on potential due to suboptimal diets have been eliminated, and that such variability will be associated with differences of growth, health, and vitality. From the point of view of nutritional research, it may be that the study of aberrant reactions, and variations of normal reactions, is the best way to obtain a more complete understanding of physiologic potential and its limitations in adjustment to diets of varying composition.

ACKNOWLEDGMENTS

I wish to express my gratitude to Dr. Isabella Leitch, Director of the Commonwealth Bureau of Animal Nutrition, who helped me to prepare this paper, and to Professor Dugald Baird, Regius Professor of Midwifery, University of Aberdeen.

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The Relationship Between Potassium Utilization and Nitrogen Balance

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THE PRESENCE of potassium deficiency in the tissues as a whole cannot be determined directly but must be inferred from such clinical findings as a decreased level of serum potassium, an abnormal electrocardiogram, or a recently developed muscular weakness. These findings presumably are the resultants of a preceding period of negative potassium balance, due either to an inadequate intake or an excessive output of the ion. Treatment usually consists in the administration of potassium salt. This ignores the fact, however, that in most instances the patient has also undergone a period of negative nitrogen balance, during which a tissue-deficit of both potassium and nitrogen has occurred.

Metabolic experiments in man have indicated that nitrogen and potassium generally follow parallel courses of excretion.[1] For example, Howard and Bigham, in a study of patients undergoing treatment for fractures, concluded that "under the conditions of these experiments, nitrogen and phosphorus move together in and out of cells, and that potassium, though with rather more leeway, follows along as a close member of the team."[2] Albright and Reifenstein came to essentially similar conclusions, viz., "that nitrogen and potassium are moving together in a fixed relationship to each other."[2]

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Presented at the *Conference on Optimal Nutrition, Its Analysis and Application*, held at the George Williams College, Chicago, Ill., April 8–9, 1955.

This work was done in co-operation with the U. S. Navy, Office of Naval Research. We also acknowledge the co-operation of the Douglas Smith Foundation for Medical Research of the University of Chicago.

In view of these indicated relationships of nitrogen and potassium under conditions of excretion, a similar relationship might be anticipated in the processes of tissue reconstruction. Moreover, in view of the fact that during catabolism both elements are being continuously excreted in the course of a continuing cellular degradation, it would not seem likely that such a process would be favorable for potassium retention, despite the liberal administration of potassium salts. In short, it seems unlikely that the therapeutic use of potassium salts is completely justified in the catabolic state; on the contrary, for purposes of nutritional repletion, it would seem that a positive nitrogen balance is a prerequisite for effective tissue utilization of potassium. It should be added, however, that even in the course of severe catabolism presumably not every cell is equally affected; therefore, not all cells should be unable to utilize potassium ion even under such adverse conditions.

Because of the many difficulties associated with metabolic studies in man designed to clarify these questions, we have subjected normal and protein-depleted adult male albino rats to varying periods of positive and negative nitrogen and potassium balances. Our purpose was to attempt to elucidate further the relationships of anabolism and catabolism to the processes determining the tissue utilization of potassium. In four experiments an effort was made to ascertain (1) the ability of protein-depleted rats to undergo effective protein repletion while eating rations containing or lacking nitrogen, and while receiving potassium salts parenterally; and (2) the interrelationships of nitrogen and potassium in normal rats similarly treated. The rations used were variants of a basal ration devoid of both nitrogen and potassium. These rations varied

TABLE I

Composition of Rations, in Per Cent

Diets ⟶	1	2	3	4	5	6
Amino acid mixture	—	11.7	—	—	—	22.75
Cellulose	5.0	5.0	6.82	5.77	9.38	9.38
Choline 50%	0.6	0.6	0.82	0.69	1.12	1.12
Corn oil	4.0	4.0	29.73	20.0	20.0	20.0
Dextrin	70.0	58.3	40.91	44.23	53.12	30.37
Oleum percomorphum	0.3	0.3	0.41	0.35	0.56	0.56
Salt mixture without K	3.73	3.73	5.09	4.30	7.0	7.0
Vitamin mixture	1.0	1.0	1.36	1.15	1.88	1.88
Water	15.67	15.67	15.27	23.86	7.5	7.5
Amount fed daily, in g	15	15	11	13	8	8

Composition of Amino Acid Mixture

DL-Alanine 4.19	L-Histidine HCl 3.25	DL-Phenylalanine 5.03
L-Arginine HCl 3.71	DL-Isoleucine 12.55	L-Threonine 3.76
DL-Aspartic acid 4.72	L-Leucine 11.68	DL-Tryptophan 1.73
L-Glutamic acid 17.77	L-Lysine HCl 9.13	L-Tyrosine 4.78
Glycine 0.37	DL-Methionine 3.80	DL-Valine 13.53

Composition of Vitamin Mixture

Nicotinic acid 0.4	Riboflavin 0.2
Calcium pantothenate 0.2	Thiamine HCl 0.1
Pyridoxine HCl 0.1	Sucrose 99.0

TABLE II

Composition of Salt Mixtures (in Per Cent)

A		*B*	
Usual Mixture		*Mixture without Potassium*	
Calcium carbonate	6.89	Calcium carbonate	7.39
Calcium citrate	30.97	Calcium citrate	33.22
Calcium phosphate, monobasic	11.33	Calcium phosphate, monobasic	12.15
Magnesium carbonate	3.34	Magnesium carbonate	3.58
Magnesium sulfate, anhydro	3.85	Magnesium sulfate, anhydro	4.13
Potassium chloride	22.40	Potassium chloride	0.00
Potassium phosphate, mono H	10.44	Potassium phosphate, mono H	0.00
Sodium chloride	0.00	Sodium chloride	18.84
Sodium phosphate, mono H, anhydro	9.40	Sodium phosphate, mono H, anhydro	19.21
Trace salts	1.38	Trace salts	1.48
Trace Salts		*Trace Salts*	
Copper sulfate	0.99	Copper sulfate	0.99
Ferric citrate	92.31	Ferric citrate	92.53
Manganese sulfate	1.15	Manganese sulfate	1.15
Potassium iodide	0.29	Sodium iodide	0.26
Potassium aluminum sulfate	0.66	Aluminum sulfate	0.46
Sodium fluoride	3.61	Sodium fluoride	3.62
Zinc chloride	0.99	Zinc chloride	0.99

with respect to amino acid content, fat content, and caloric potentials. Their compositions are given in Tables I and II, together with those of the amino acid mixtures, the vitamin mixture, and the salt mixtures used. The animals (Sprague-Dawley) were kept in metabolism cages, with collections of urine and feces daily or on alternate days. For the potassium determinations a Janke Internal Standard Flame Photometer was used. The nitrogen determinations were made by a micro-Kjeldahl procedure.

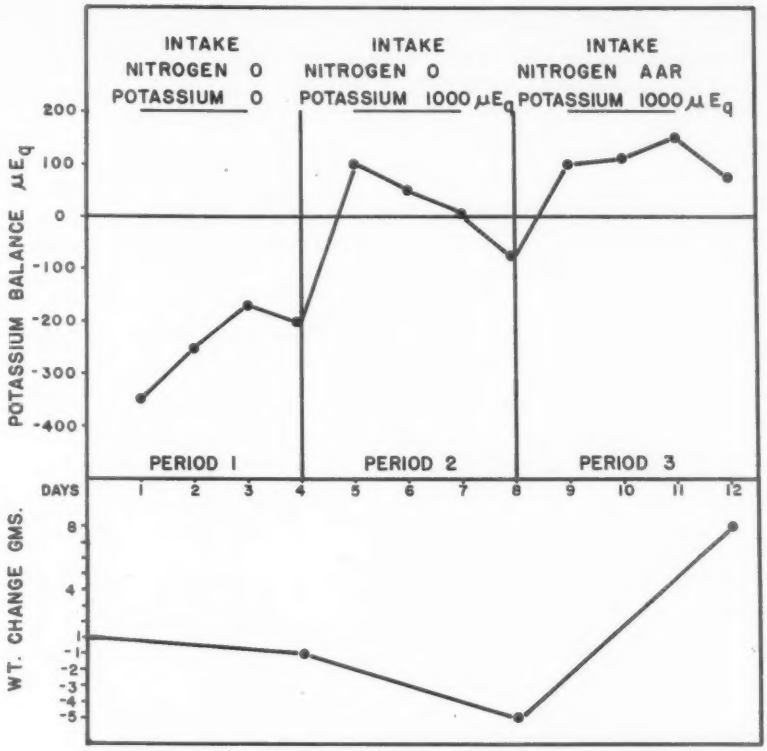

Fig. 1. Potasssium balances and weight changes in protein-depleted rats with varying intakes of nitrogen and potassium.

EXPERIMENTS

Experiment 1

In the first experiment, five protein-depleted rats underwent potassium balance determinations during three successive, four-day, diet periods as follows: In period 1, 15 grams of ration No. 1 were fed daily; in period 2 this ration was continued in conjunction with subcutaneous injections of a solution of potassium chloride, 250 microequivalents per day; in period 3 the ration supplemented with the amino acid mixture (ration 2) was used and the injections of potassium chloride were continued. The results with reference to weight changes and potassium balances are shown in Figure 1.

In period 1 there was a slight loss of weight, a reduction in consumption of the ration (approximately 20 per cent) and a continuous negative potassium balance. In period 2, during which potassium chloride was being injected, and while weight loss was continuing the potassium balance became positive on the first day but then decreased, becoming negative on the fourth day. In period 3, during which the amino acid ration was fed, the rats immediately began to gain weight, ate the ration completely, and went into positive potassium balance. It should be added that the decision to inject 250 microequivalents of potassium daily was based on earlier experiments which had demonstrated that under similar conditions of nutritional repletion approximately 20 milligrams of potassium chloride daily sufficed to ensure optimal repletion.[3]

Experiment 2

In order to compare the findings of the preceding experiment with those which might occur in well-nourished animals, ten normal rats,

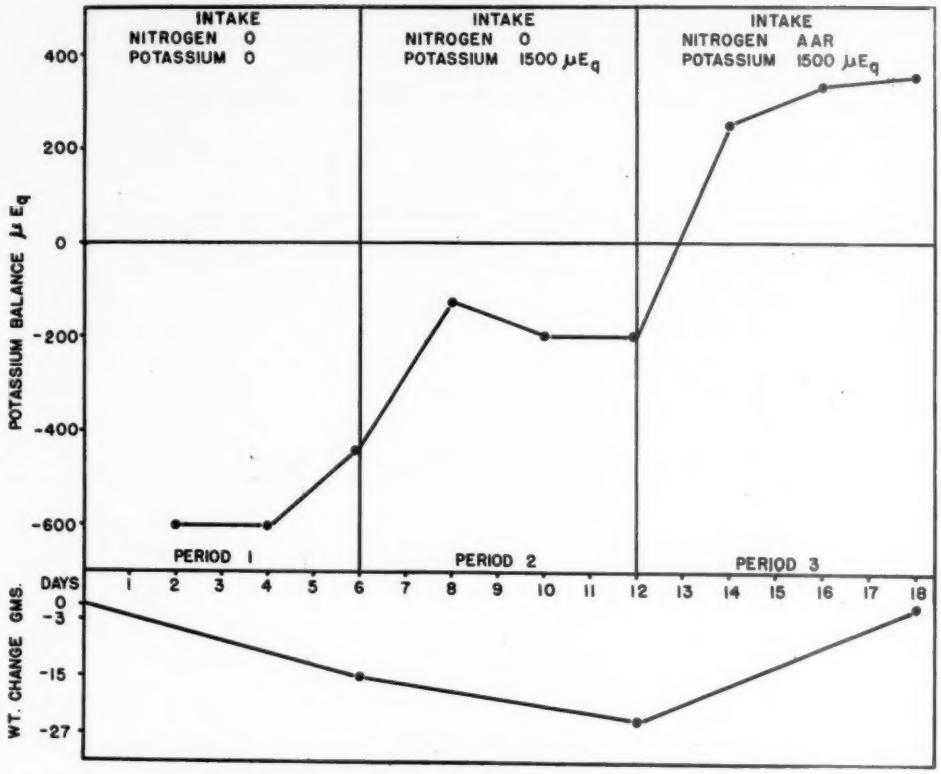

Fig. 2. Potassium balances and weight changes in normal rats with varying intakes of nitrogen and potassium.

whose weights ranged between 229 and 246 grams, were fed the test rations in three metabolic periods of six days each. Potassium balances were determined as before. These animals were fed rations 3 and 4, of higher fat content than ration 1, in order to minimize "food-scattering." Ration 4 was used only because ration 3 contained too much fat for convenience in measuring diet intakes. Both rations, however, were isocaloric. In period 3 the amino acid ration 2 was fed.

The results (Fig. 2) demonstrate that in period 1 all animals receiving ration 3 remained in negative potassium balance and all lost weight. The injection of potassium chloride in period 2 again failed to induce positive potassium balances and the animals continued to lose weight. In period 3, however, when the amino acid ration 2 was fed while potassium was being administered, the animals all started to gain weight and all went quickly into positive potassium balance.

Experiment 3

In order to ensure as completely comparable conditions as possible with respect to food intake, five additional normal rats were subjected to forced feeding over four metabolic periods of four days each during which both nitrogen and potassium balances were determined. As a preliminary step each animal was accustomed gradually to the procedure, starting with intragastric feedings, twice daily, of 3 ml of ration 5 suspended in an equal quantity of distilled water, and increasing the amounts daily until, by the fifth day, all were receiving the amounts necessary to ensure ingestion of the complete ration during the metabolic studies. The results of the balance studies are shown in Figure 3.

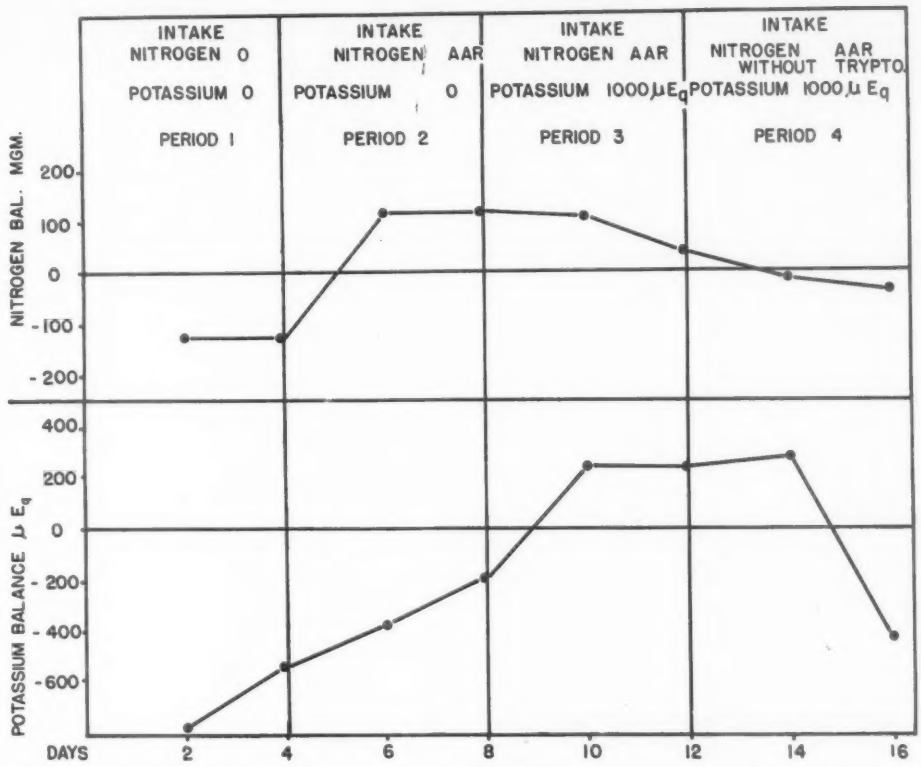

Fig. 3. Nitrogen and potassium balances in normal rats force-fed with varying intakes of nitrogen and potassium.

Thus, in period 1, with the animals receiving basal ration No. 5, devoid of potassium and nitrogen, all remained in both negative nitrogen and potassium balance. In period 2, when approximately 1.8 grams of amino acid mixture daily replaced an equal amount of dextrin in the ration, but in which potassium was still lacking, the animals went into positive nitrogen balance. The potassium balances, however, remained negative, although somewhat less so than in period 1. In period 3, during which 250 microequivalents of potassium were added to the ration, the animals remained in positive nitrogen balance and also went into positive potassium balance. Finally, in period 4, one essential amino acid (tryptophan) was omitted from the amino acid mixture in order to induce a catabolic state. All the animals went promptly into negative nitrogen balance, followed, after a two-day lag, by a negative potassium balance.

Experiment 4

In the final experiment, ten protein-depleted rats were fed test-rations 1 and 2 in four diet periods of six days each, with nitrogen and potassium balances being determined as before. The results are shown in Figure 4. The purpose of this experiment was to determine whether or not considerably larger intakes of potassium might have a greater influence upon the possible attainment of a positive potassium balance.

As can be seen in the chart, all animals receiving rations devoid of nitrogen and potassium in period 1 remained in negative nitrogen and potassium balance. This ration was continued throughout period 2, but with the animals being divided into two groups. Those in one group received a daily supplement to the ration of one milliequivalent of potassium; those in the other group received two and one half milliequivalents. All, however, continued

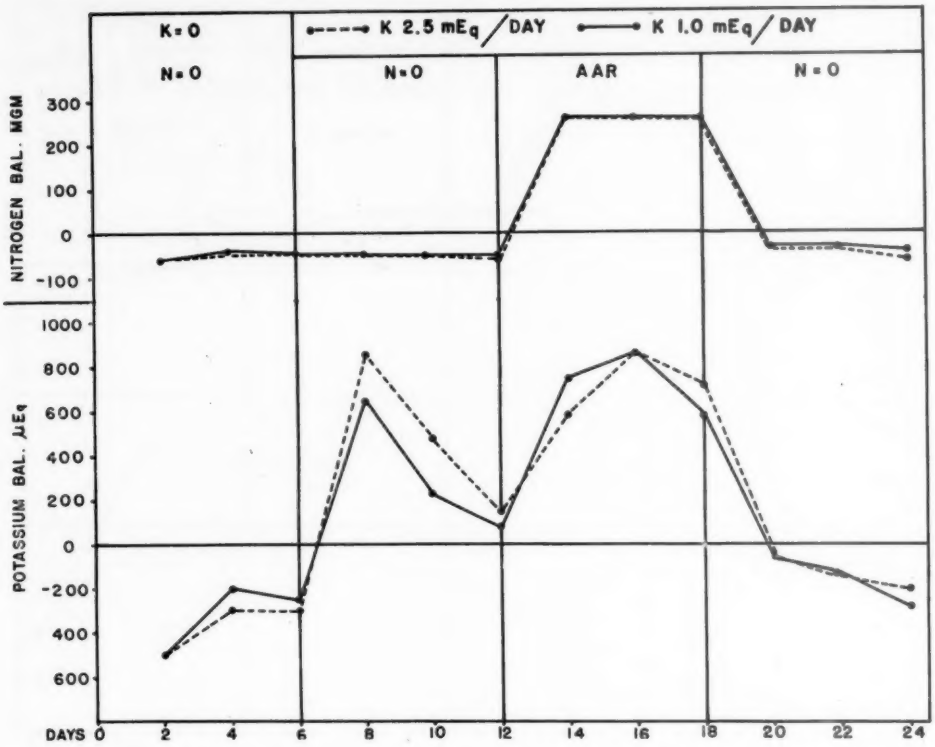

Fig. 4. Nitrogen and potassium balances in normal rats with varying intakes of nitrogen and with large intakes of potassium.

in negative nitrogen balance, but with the larger intakes of potassium, the potassium balances became positive on the second day, only to decrease progressively, approaching the zero line with the third collection sample. In period 3, when anabolism was established by feeding the amino acid ration 2, all animals gained weight, and both nitrogen and potassium balances became strongly positive, remaining so throughout the period. In period 4, when ration 1 devoid of nitrogen was again fed, but with the continuation of intakes of potassium chloride, the animals lost weight slowly and went into both negative nitrogen and potassium balance.

DISCUSSION

These experiments strengthen the point of view that the problem of correcting a potassium deficit is a more complicated one than can be solved simply by the administration of a potassium salt. On the contrary, they indicate that the metabolic state of the tissues largely determines their ability to retain and to utilize potassium ion; they demonstrate, also, that for optimal nutritional replenishment of depleted tissues both nitrogen and potassium are essential, and in a definite relationship to one another. Elevation of the serum potassium level by the administration of potassium alone is not enough, presumably because of the fact that the loss of tissue mass, whether from starvation or as a result of catabolism in general, creates a tissue need for both nitrogen and potassium. Moreover, if tissue loss is actively proceeding as a consequence of a marked catabolic state, it is unlikely that potassium alone can be used effectively by tissue cells for purposes of cellular reconstruction. The basic nutritional problem in such a situation, therefore, would seem to be that of re-establishing an anabolic state. Once this

has been accomplished, potassium utilization by cells should quickly follow.

Unfortunately, in surgical patients conditions often exist which contribute to losses of potassium. These may include dehydration and inanition, as well as losses through renal and gastrointestinal routes. Randall and coworkers[4] have shown that such simple procedures as the administration of salt solution, or glucose and amino acid solutions, may initiate diuresis with a further loss of potassium from cells. Elman and associates[5] have also suggested that postoperative loss of potassium may result from hyperactivity of the adrenal cortex, due both to the excretion of potassium and the retention of sodium. Finally, although transitory retention of potassium may be accomplished in surgical patients even while they are in negative nitrogen balance, as has been shown by Howard and Carey,[6] our results (fourth experiment) indicate that even with comparatively large potassium intakes, but in the presence of a continuing negative nitrogen balance, potassium retention was at best transient, and became continuous only as the animals went into positive nitrogen balance.

SUMMARY AND CONCLUSIONS

Experiments were performed in normal and in protein-depleted adult rats, in an effort to determine the metabolic relationships between positive and negative nitrogen balances and the capacity of the tissues to retain dietary potassium. When the animals were fed synthetic rations devoid of both nitrogen and potassium, weight losses ensued and the potassium and nitrogen balances were negative. The administration of potassium chloride to such animals while they were eating a nitrogen-free ration failed to establish positive potassium balances or to promote weight-gains, whereas the addition to such rations of an appropriate amino acid mixture caused the animals to go into positive nitrogen and potassium balances. Following the elimination of one essential amino acid (tryptophan) from such a mixture, however, the animals went quickly into negative nitrogen and potassium balance. Finally, the feeding of the complete amino acid ration devoid of potassium led to the development of a positive nitrogen balance but a continued negative potassium balance; and increasing the intake of potassium by as much as ten times the amount necessary for adequate repletion seemed to have only a transient effect in achieving a positive potassium balance during catabolism.

These experiments emphasize the importance of anabolism in relation to the overall utilization of dietary potassium. They suggest, also, that in the presence of a general catabolic state, tissue retention of dietary potassium is impaired, and that for optimal cellular utilization of potassium for purposes of tissue synthesis, the anabolic state is an essential requirement.

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Optimal Nutrition Correlated With Nitrogen Retention

By JAMES B. ALLISON, PH.D.*

THE SO-CALLED labile protein stores of the body are continually entering into catabolic processes leading to oxidation of the amino acids and to the excretion of urea. It is the purpose of this paper to correlate the magnitude of these stores, together with their catabolic activity, with responses of the living system to various nutritional stresses. This correlation will be presented through nitrogen balance and through changes in the plasma and other tissue proteins.

NITROGEN BALANCE

As the labile protein stores are depleted through illness or malnutrition, the catabolic activity may decrease to a minimum, thereby decreasing the excretion of urea nitrogen and conserving tissue proteins. If an animal is placed on a protein-free diet, the excretion of urea nitrogen gradually decreases to a low and to a minimum value. Such a decrease in nitrogen during a period of feeding a protein-free diet to dogs is idealized in Figure 1. The overall excretion of nitrogen was reduced asymptotically to approximately 1 g/day/m^2 of body surface area and the labile protein stores in the plasma and in the tissues were correspondingly depleted. Further feeding of the deficient diet would continue the depletion without markedly decreasing the excretion of nitrogen, until finally an irreversible destruction of tissue would occur leading to an increased excretion of nitrogen. If, before that irreversible stage is reached, a constant daily protein intake is fed, the animal goes into positive balance, so that continued feeding of this amount of protein refills the protein stores, the nitrogen balance gradually dropping to equilibrium. This daily intake of nitrogen is now required to maintain equilibrium. The gradual filling of the protein stores with concomitant increase in catabolic activity is illustrated by the dotted line in Figure 1.

Repletion, as it is illustrated by nitrogen balance in this figure, takes place in the presence of a pattern of dietary amino acids which is favorable for anabolic processes, every tissue being in positive balance so that the stores are filled uniformly. Egg protein provides such a pattern of amino acids. The importance of a proper pattern of essential amino acids[1] for the development of tissue proteins is illustrated in the rat repletion studies by Cannon and his associates.[2,3] They have calculated the approximate daily requirements for the essential amino acids for recovery of weight in the depleted rat, thereby demonstrating that the ratios between the acids are similar to those found in whole egg protein. An imbalance of amino acids in the diet can lead, on the other hand, to an imbalance in tissue proteins.[4]

NITROGEN BALANCE INDICES

The relationship between nitrogen balance and absorbed nitrogen is linear in the region of negative balance, the linearity extending into the region of positive balance if growth in tissue nitrogen is taking place. Line B in Figure 2 illustrates the type of data obtained on an

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Presented at the *Conference on Optimal Nutrition, Its Analysis and Application*, held at the George Williams College, Chicago, Ill., April 8–9, 1955.

Some of these researches were made possible by an Institutional Grant from the American Cancer Society.

adult dog with full protein stores and fed a protein of high nutritive value. The excretion of nitrogen arising from catabolism of tissue proteins was high, equivalent to 4 g/day/m² of body surface area. The same amount of dietary nitrogen was required to maintain equilibrium to replace the loss through catabolism of tissue proteins. Curve A illustrates similar data obtained on this animal fed a protein with a pattern of amino acids less well balanced for anabolism. More dietary nitrogen was needed to maintain equilibrium, the excess amino acids not used for anabolism being oxidized to increase the excretion of urea nitrogen in the urine. Thus the slopes of these lines are a function of the nutritive value of the protein, the slope decreasing as the nutritive value decreases. These slopes have been called the nitrogen balance indices of the dietary protein.[5] The indices are the fractions of absorbed nitrogen retained in the body of the animal, provided the excretion of nitrogen during nitrogen-free feeding represents a constant catabolism of tissue nitrogen, independent of dietary intake. Mitchell has developed admirably this concept of the "biological value" of proteins.[6]

Curves C and D (Fig. 2) illustrate data obtained when the labile protein stores were somewhat reduced, less dietary nitrogen being needed to maintain equilibrium. The curves extend into the range of positive balance. Curve E illustrates data obtained while feeding a protein of high nutritive value to a dog markedly depleted in protein stores. Such an animal can be placed far into positive balance and the slope of the line is increased, demonstrating the increased anabolic activity associated with the depleted state. Thus the magnitude of positive balance that can be produced and the rate of utilization of a pattern of amino acids are functions of the degree of depletion.

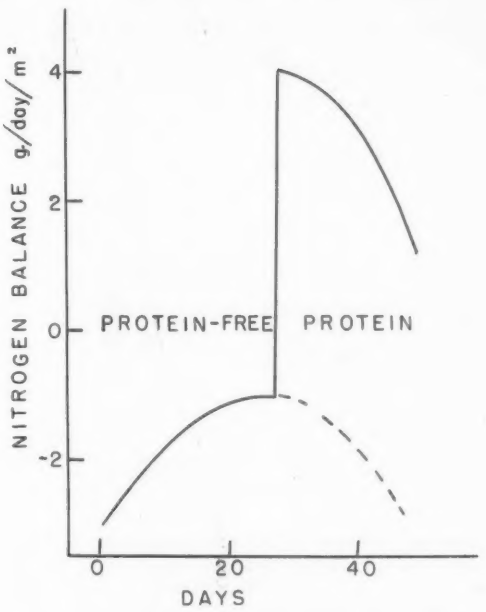

Fig. 1. Data illustrating variation of nitrogen balance in dogs fed a protein-free diet, followed by protein equivalent to 0.35 gram of casein nitrogen/day/kg body weight.

CALORIES

The curves in Figure 2 were all obtained while feeding an adequate caloric intake, which in these dogs would be approximately 3000 calories/day/m².[7] In an animal with high protein stores, even a slight reduction below this

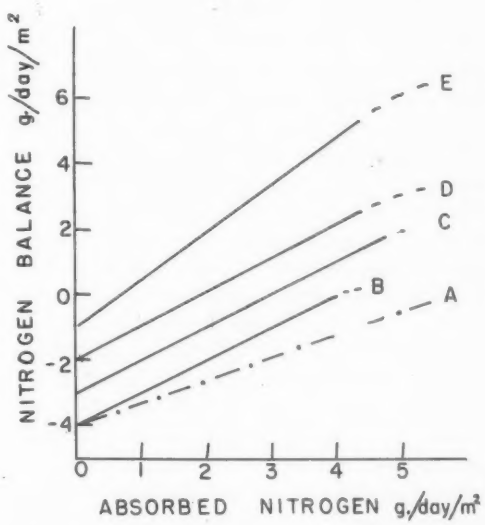

Fig. 2. The relationship between nitrogen balance and absorbed nitrogen in dogs with different degrees of catabolic activity of labile protein stores. (See text.)

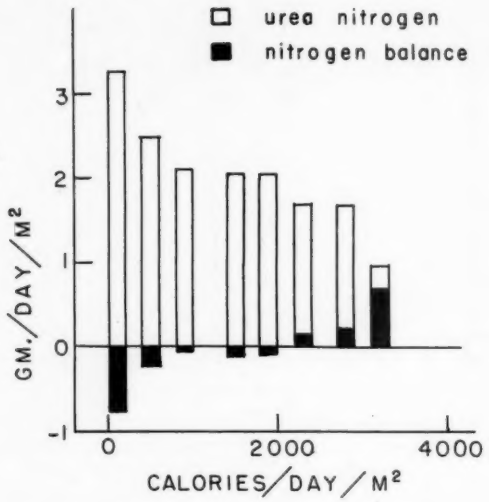

Fig. 3. Variation in the excretion of urea nitrogen and in nitrogen balance in dogs fed a constant protein intake but a variation in caloric intake. (Data taken from Rosenthal and Allison[7].)

optimum increases the excretion of urea nitrogen, thereby reducing nitrogen balance. The net result is to push curves such as A, B, C down on the y axis, decreasing nitrogen balance but not altering the slopes.

The effects of varying caloric intake on the excretion of urea nitrogen and on nitrogen balance of dogs fed 3.82 g of casein nitrogen/day/m^2 of surface area are illustrated in Figure 3.[7] The white bars record the excretion of urea nitrogen, the black bars record nitrogen balance. A decrease in calories from 3000 to 2000 increased the catabolic activity of the tissue proteins, increasing the amount of dietary nitrogen needed to maintain equilibrium but not altering the nutritive value of the diet as measured by nitrogen balance indices. A reduction below 1000 calories resulted in a decrease in the index, thereby lowering the nutritive value of the dietary protein to the point where it was impossible to reach nitrogen equilibrium. These results were obtained in dogs that were permitted to adapt activity and performance to restricted caloric intakes. If activity had been kept high, the excretion of urea would have increased more rapidly and nitrogen balance would have become more negative with caloric restrictions. In active animals, a caloric restriction to less than 50 per cent of so-called optimum can result in a condition where nitrogen equilibrium cannot be attained. On the other hand, data have been presented to demonstrate anabolic activity at very low caloric intakes,[9,10] the magnitude of anabolism being a function, in part, of the magnitude of the protein stores. Spector and Calloway,[11–13] in a study of the influence of standardizing diet on nitrogen retention during restriction in calories, found that the nitrogen and body weight loss were varied with the standardizing diet during the first few days of restriction in calories (50 per cent of normal). Ultimately, all groups lost approximately the same amount of protein.

The reduced catabolic activity in the depleted animal is correlated with a lower caloric demand for nitrogen retention. A normal animal fed 3 g of nitrogen/day/m^2 but with a reduced caloric intake of 500/day/m^2 would be in negative balance. Another animal depleted in labile protein stores with the same caloric intake and nitrogen intake would be in positive balance. Continued feeding, however, of a caloric deficit over a relatively short period of time to the depleted animal results in depletion of essential tissues, throwing the animal into negative balance and into a serious crisis. The dog with ample stores, on the other hand, will maintain essential tissues even in negative balance for periods of as long as 90 days before approaching the same crisis.[7,8]

AMINO ACID BALANCE

The catabolism of tissue protein stores is a function of their magnitude, correlated with shifts in the demands of intermediary metabolism. In rats and dogs, the sulfur amino acids are particularly effective in reducing the catabolism of tissue proteins and promoting anabolic processes. For example, methionine, added to a protein-free diet or to a diet containing protein deficient in sulfur will reduce the excretion of urea nitrogen.

The data, illustrated in Figure 4, were obtained on two groups of dogs fed 3 g of casein

nitrogen/day/m² of body surface area.[14] DL-Methionine was added as a supplement to the diet of each group after a period of feeding the unsupplemented diet. The data in this figure represent average excretion of urea nitrogen (white bars), of ammonia nitrogen (lined bars), and of creatinine (black bars) over a four-day collection period. Addition of methionine to the diet reduced the excretion of urea but did not alter the excretion of creatinine or ammonia. The fact that methionine reduced the excretion of urea in animals fed a protein-free diet and diets low in sulfur amino acids suggests that this amino acid is involved in catabolism of labile protein stores. There is no correlation, however, with certain basic endogenous catabolic processes leading to the excretion of creatinine. The suggestion has been made that the formation of creatinine is a function of the number of active nuclei of the soft tissues of the body, a function which is fixed genetically and is not influenced by the rise and fall of labile protein stores, which are largely cytoplasmic in origin.[15] The excretion of creatinine, however, can be altered by excesses of methionine, especially in the presence of glycine or guanidoacetic acid, a result which can be explained through an increase in concentration of precursors of creatinine.[16–18]

Perhaps excess tissue proteins are catabolized in animals fed a protein-free diet or a sulfur-deficient protein diet to provide sulfur amino acids for growth of fur.[6] Methionine, however, may be used in other pathways leading to conservation of tissue protein. For example, the excretion of urea is reduced still further if glycine or guanidoacetic acid is added with the methionine to the protein-free diet.[19] Supplementation with glycine illustrates the possible direction of methionine into other pathways.[18] The data recorded in Figure 5 demonstrate the dramatic effect glycine has upon methionine supplementation of a low casein diet. The first white bar over nitrogen records the negative balance produced in rats fed a restricted intake of a diet containing 12 per cent casein. These animals were also in negative sulfur balance, as illustrated by the white bar over sulfur. Adding 4.8 per cent

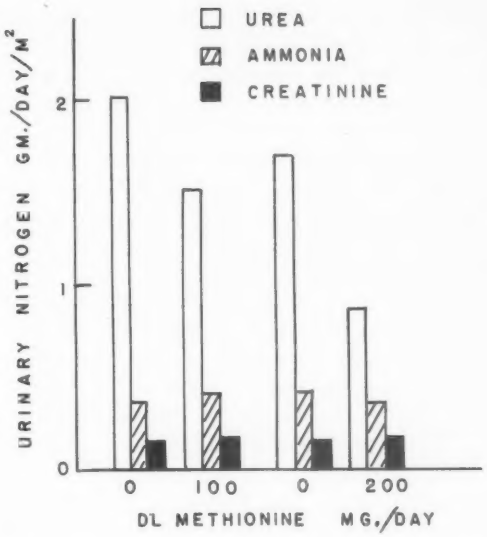

Fig. 4. Data obtained on two groups of dogs fed a constant amount of casein nitrogen with and without added DL-methionine. (See Allison *et al.*[14])

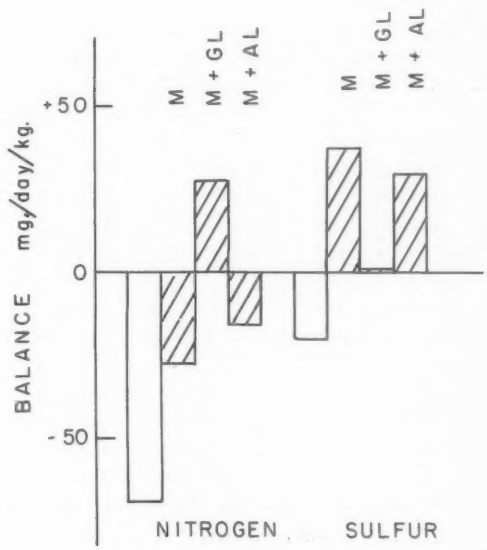

Fig. 5. Data obtained on rats pair-fed 12 per cent casein diet with and without added methionine (M), methionine plus glycine (Gl), and methionine plus alanine (Al). (Data obtained from Roth, Allison and Milch[18].)

DL-methionine to the diet put the animals well into positive sulfur balance and reduced the negativity of the nitrogen balance, as recorded by the first lined bars (M). This amount of methionine was considered an excess, creating an imbalance toward sulfur retention. Adding 4.8 per cent glycine with the methionine reduced the sulfur balance to equilibrium and placed the animals into positive nitrogen balance as recorded by the second lined bars (M + GL). Both glycine and glycocyamine, when added in proper amounts with methionine, reduced the excretion of urea under conditions of depletion.[19] Studies by Brush, Willman, and Swanson[20] demonstrated that all of the essential amino acids, except phenylalanine, valine, and tryptophan, under some conditions have tissue nitrogen sparing action in the rat.

LIVER PROTEINS

Internal shifts in tissue proteins associated with amino acid imbalances can be illustrated in experiments where large excesses of methionine are added to the diet of rats. Such imbalances resulted in hypertrophy of the kidney and a relative increase in liver protein.[21] Relative increases in liver protein have also been noted in other conditions of amino acid imbalances.[22] Campbell and Kosterlitz[23] found that diets deficient in single amino acids or in calories did not reduce labile protein stores in the liver as rapidly as a protein-free diet. They also reported that liver cytoplasm could be formed in the absence of dietary lysine. The overall nitrogen balance of an animal is the sum of gains and losses from the various tissues of the body, so that it is possible for a tissue to be in positive balance while the body, as a whole, is in negative balance, or the body, as a whole, may be in positive balance while some tissues are losing nitrogen.[4] An exaggerated example of a tissue in positive balance while other tissues are in negative balance is often found in tumor-bearing animals. The animal with the tumor may be in overall positive balance because of the marked positive balance of the tumor, although other tissues of the body are in negative balance and are losing nitrogen.[24–27] Under these conditions, the liver may also remain in positive balance, possibly reflecting an amino acid imbalance created in the body of the animal by the growing tumor (see Figs. 6 and 7).

In many nutritional experiments, however, the liver shifts in balance directly with the body as a whole, the cytoplasmic proteins of the liver cells being considered the most labile of all tissues. Kosterlitz and Campbell and associates[23] and others[28–31] have presented experimental designs which make it possible to correlate nutritive value of dietary proteins with their ability to form labile liver proteins.

ENZYME SYSTEMS

Others have shown[33–35] that depletion in liver proteins resulted in the reduction in the activity of many enzyme systems, an imbalance that leads to an altered metabolism. This altered metabolism, for example, affects the ability of the liver to detoxify and protect the animal against certain types of stresses. An indirect measure of the activity of liver enzyme systems can be illustrated by the excretion of products of oxidation of the carcinogen 2-aminofluorene in the urine of the dog.[36] The data indicate that 2-aminofluorene is converted into more and more polar diazotizable substances during this process of oxidation leading to a heat-labile, water-soluble derivative before a final detoxication. The amount of this heat-labile product excreted is correlated with the toxicity of the drug; the smaller the amount, the more complete is its oxidation and the less toxic it is to the animal. The excretion of this derivative under various dietary regimens is illustrated in Figure 8. The first bar records the relatively high excretion in animals fed a protein-free diet containing an amount of riboflavin considered adequate for normal growth in dogs. Riboflavin is included with protein in the experimental design because this vitamin plays an important part in the development of the labile protein stores of the liver. When the dogs were fed sufficient casein (6.3 per cent) in the diet to maintain equilibrium, but were deficient in riboflavin, the excretion of the

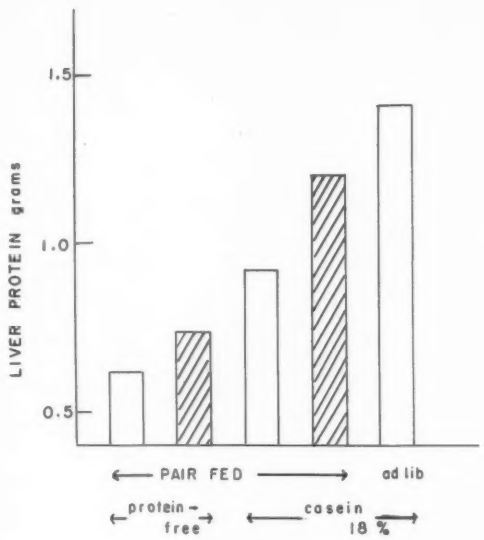

Fig. 6. Liver protein in control (white bars) and in tumor-bearing rats (lined bars). (Data taken from Allison, Bernstein and Babson[24].)

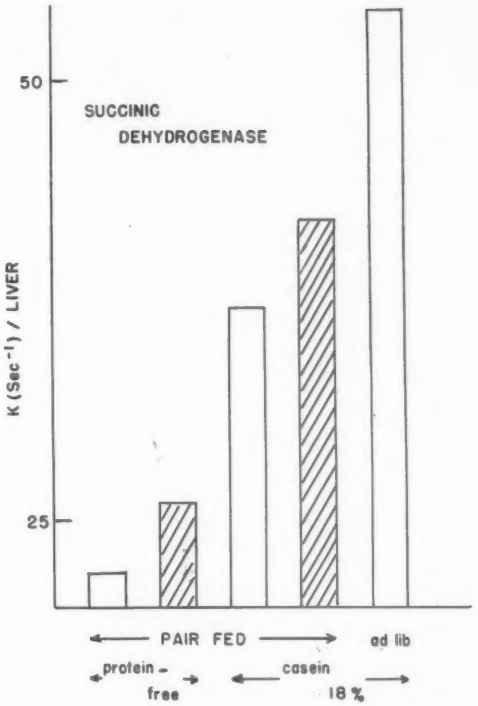

Fig. 7. Succinic dehydrogenase activity in liver in control (white bars) and in tumor-bearing rats (lined bars). (Data taken from Allison, Bernstein and Babson[24].)

heat-labile material was still high. Adding the so-called normal requirement of riboflavin with the 6.3 per cent casein reduced the excretion to 1.34 mg/day/kg of body weight. Adding excess riboflavin reduced the excretion still further to 0.38 mg. Keeping the riboflavin content low and equal to 0.025 mg/day/kg, but increasing the casein to 25 per cent, resulted in an excretion of 0.94 mg; but if excess riboflavin was added with the high protein diet the excretion of the heat-labile substance was eliminated, indicating maximum oxidation of the drug and producing minimum toxicity.

Acetylation of the 2-aminofluorene appeared to be a step in the oxidation and detoxication process. It was found that increasing pantothenate in the diet raised the excretion of the acetylated amine and reduced the excretion of the heat-labile, water-soluble amine. Thus, a high protein diet, particularly when supplemented with the vitamins that would lead to maximum development of the enzyme systems of the liver, had a marked protective effect—a protective effect which will be mentioned again in connection with another drug. The maximum development of enzyme systems is, of course, a function of all constituents of the diet, a fact which emphasizes the importance of balance between these constituents.[37–39]

PLASMA PROTEINS

Plasma albumin is one labile protein store in the body which seems to be most uniformly depleted, whatever the cause of depletion. Electrophoretic patterns were determined in normal rats fed a 12 per cent casein diet, in rats depleted in proteins by feeding a protein-free diet, and in tumor-bearing rats. These results are illustrated in Figure 9. Plasma albumin (black bars) was reduced in the animals depleted by low nitrogen feeding or by the

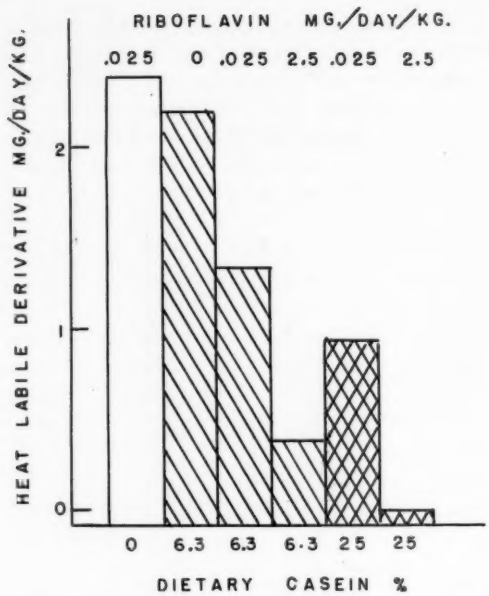

Fig. 8. Urinary excretion of heat-labile derivative of 2-aminofluorene in dogs fed different amounts of casein and riboflavin. (Data taken from Allison, Wannemacher, and Migliarese[33].)

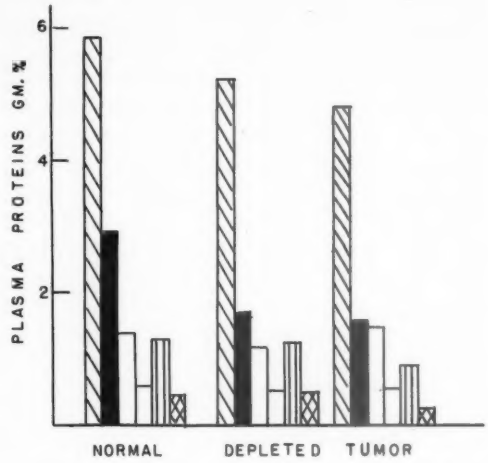

Fig. 9. Electrophoretic patterns of plasma from normal, protein-depleted, and tumor-bearing rats. Total protein (bars with slanted lines), albumin (black bars), alpha globulins (white bars), beta globulins (bars with vertical lines), gamma globulins (bars with crossed lines).

tumor, the globulins remaining near normal. Thus, even though liver proteins and enzyme systems may remain relatively high in the tumor-bearing animal, the plasma albumin, probably formed in the liver, is markedly reduced by the growing neoplasm.

Another characteristic change, resulting from either type of depletion, was an increase in polarographic activity, presumably associated with sulfhydryl groups.[40] The proteins seem to be held together more loosely, more polypeptide fractions being left in the filtrate, when the plasma proteins of the depleted animals are precipitated with sulfosalicylic acid. These fractions also have a higher than normal polarographic activity, results which suggest some further correlation between depletion and sulfur metabolism.

All these data emphasize the value of the concept developed by Whipple, Madden, Robscheit-Robbins, Miller, and associates[41] of an ebb and flow of protein nitrogen from one tissue to another. This concept, made more real through the isotopic studies of Schoenheimer, Rittenberg, and others,[42] suggests that all tissue proteins may be considered to draw from a series of integrated metabolic pools. The labilities of the tissue proteins vary from those which are rapidly depleted to those which are maintained at the expense of the more labile stores. Some tissue proteins may be more like one-way streets, taking from but contributing little to metabolic pools. The proportions of less labile proteins may be quite high in some rapidly growing and active cells and may be exaggerated in such tissues as neoplasms.

TUMOR-HOST RELATIONSHIPS

Some neoplasms grow, drawing from and contributing to the metabolic pools of the body in a way similar to normal tissues. Such tumors are reduced in growth rate, for example, when the animal is fed a protein-free diet. Other tumors will grow almost as well in an animal fed a protein-free diet as in one receiving a high protein intake. Such tumors are very malignant nutritionally, growing independently of the diet and at the expense of the rest of the tissues of the body.

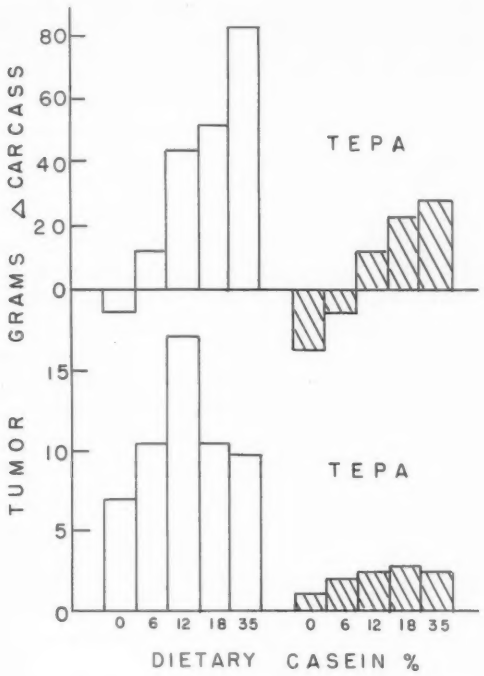

Fig. 10. Growth (14 days) of tumor and carcass (white bars) in rats transplanted with a sarcoma and fed different amounts of casein in the diet. The inhibitory effects on growth of both tumor and carcass of triethylenephosphoramide (TEPA) are illustrated by the lined bars. The drug was given five days after transplantation, at which time the tumor was well established.

The following data were obtained in rats in which a transplanted sarcoma of the nutritionally malignant type was growing. A study of the growth characteristics of this sarcoma demonstrated that it had an induction period of several days, during which time there was development of the primary vascularization process. Following this induction period, the tumor grew semilogarithmically until it had reached a maximum size of about 15 to 20 grams, by which time the depletion of the rat had become very severe. The induction period was shortest in animals fed 12 per cent casein in the diet, so that the tumor reached maximum size sooner on this diet than on any other containing less or more casein. The overall optimum development of this sarcoma on the diet containing 12 per cent casein is illustrated in Figure 10. The short induction period on the 12 per cent casein diet was found to be associated with methionine. Increasing the methionine content of the diet lengthened the induction period to one equivalent to that observed in animals fed high casein diets.[43] The longer induction periods associated with low casein or protein-free diets may be the result of a tendency to conserve sulfur amino acids in the depleted state.

The normal tissues of the body may be grouped under the word "carcass." The increase in the weight of the carcass with increase in protein intake is illustrated also in Figure 10. Thus the animal fed a high protein diet has a high Δ carcass/tumor ratio, the magnitude of which is a measure of the welfare of the whole animal. Such animals survive much longer and are more receptive to therapy.

The ethylenimino derivatives such as triethylenephosphoramide (TEPA) if given in sufficient doses will slow up the growth of all tissues of the body, reducing food efficiency. The effect of giving TEPA (1 mg/day/kg of body weight) on the growth of the sarcoma is illustrated in Figure 10. The amount of casein in the diet had little effect upon chemotherapy of the tumor, but increasing casein intake had a marked protective effect on the carcass. With a low protein diet the depleting effect of TEPA on the carcass was so marked that the animals were not helped by the therapy, even though the growth of the tumor was restricted. With the high protein diet the growth of the carcass was so favored that the therapy could be continued until some regression of the tumor took place. Further work has demonstrated that supplementation with methionine or, still better, methionine plus glycine or guanidoacetic acid under conditions of food restriction can protect the carcass from both the depleting effect of the tumor and the drug, making a valuable combination of nutritional therapy and chemotherapy.[44]

The application of methionine supplementation to the protection of the carcass in tumor-bearing rats fed a 12 per cent casein diet is

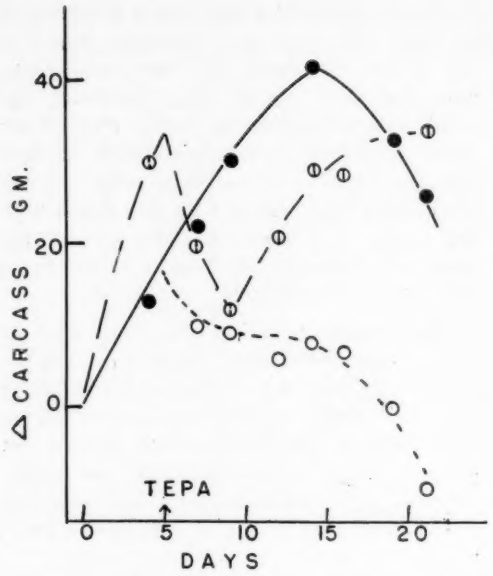

Fig. 11. The growth of carcass in tumor-bearing rats fed 12 per cent casein in diet (black circles), in tumor-bearing rats fed the same diet but given TEPA (1 mg/day/kg of body weight) five days after transplantation (white circles), in tumor-bearing rats fed casein supplemented with methionine and given TEPA therapy (circles with bars).

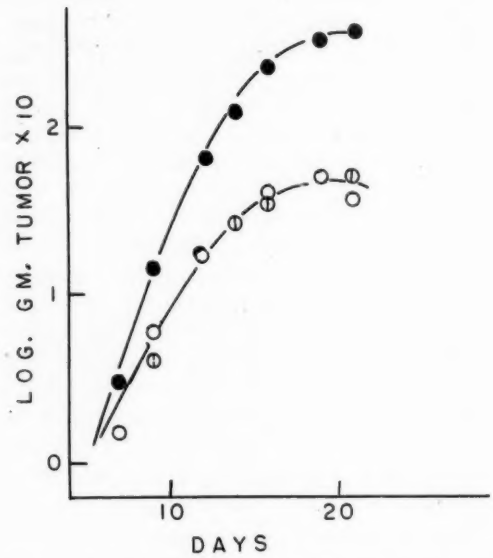

Fig. 12. The growth of tumor in same experiment illustrated in Figure 11.

illustrated in Figure 11. The black circles represent the growth of the carcass in the rats fed the 12 per cent casein diet without therapy. The drug, TEPA, was given (1 mg/day/kg body weight) to another group fed the 12 per cent casein diet after the tumor had started in the semilogarithmic growth phase (dotted line through open circles). Another group was fed the 12 per cent casein supplemented with 0.67 per cent methionine and given TEPA therapy (dash line through circles with vertical bars), demonstrating the marked protective effect of methionine to the carcass. The growth of the tumor is illustrated in Figure 12, the black circles recording the growth without therapy, the white circles that with therapy. Thus TEPA reduced the growth of the tumor, a reduction that was independent of the diet. The net result was a high Δ carcass/tumor ratio in animals fed the methionine-supplemented diet and given TEPA therapy, a condition favorable to the development of the labile protein stores of the body and to the ultimate regression of the tumor.

SUMMARY

Experiments with rats and dogs indicate that the sulfur amino acids are particularly effective in reducing the catabolism of tissue proteins and promoting anabolic processes. This may reflect in part the increased requirement of these amino acids in these hairy species.

Overall nitrogen balance is a measure of the sum of gains and losses from the various body tissues, but may not indicate the shifts of protein nitrogen from one tissue to the other. An exaggerated example of a tissue in positive balance while other tissues are in negative balance is often seen in tumor-bearing animals.

The liver, being a very labile tissue, makes it possible to correlate the nutritive value of dietary proteins with their ability to form labile liver proteins. This may also be expressed as the measure of liver enzyme activity under the influence of dietary protein. Maximum elimination and minimum toxicity of the compound 2-aminofluorene developed when an excess of riboflavin was added to a high protein diet. Furthermore, increasing the amount

of pantothenic acid in the diet resulted in an increased acetylation of 2-aminofluorene. Thus an adequate protein diet, especially one supplemented with vitamins, leads to the maximum development of enzyme systems in the liver.

The ethylenimino derivative, triethylenephosphoramide (TEPA), will depress the growth of all body tissues.

With an adequate protein diet the growth of the carcass was so favored that the therapy could be continued until some regression of the tumor took place. Supplementation of the diet with methionine under conditions of food restriction protects the carcass both from the depleting effect of the tumor and the drug, thus offering a valuable combination of nutritional and chemotherapy.

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Postabsorptive Undulations and Oscillations in Blood Glucose

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THE postabsorptive blood glucose level is normally never static for longer than a few moments at a time.[1,2,3] It is constantly changing. This fact was strikingly brought to our attention by the necessity for precise determinations of the true fasting blood glucose level in connection with carrying out in humans the six-minute test° for responsiveness to insulin.[4,5,6]

Single readings of fasting blood glucose were found to vary so strikingly from minute to minute and to be so nonreproducible, even in samples taken only two minutes apart, that a reasonably accurate estimation of the postabsorptive glucose level could be determined only by establishing the mean glucose value of at least three or four consecutive samples of blood taken at two-minute intervals. The striking variations from reading to reading, which usually extended far beyond the standard error△ incidental to the method used, stimulated this inquiry into: (1) the frequency with which the phenomenon of significant variation at short time intervals is to be found in man and in dogs; (2) the mechanism producing the spontaneous fluctuations which were observed. Postabsorptive venous blood glucose was, accordingly, studied in 100 unselected individuals, among whom were included diabetic subjects and nondiabetic normal persons, as well as nondiabetic obese people. These subjects were unselected save that an effort was made to study only those individuals who by experience were undisturbed by venipuncture.

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The essayists desire to express their gratitude to Mrs. Agnes C. Dann for her invaluable assistance in carrying through all of the blood glucose determinations involved in this study.

° In brief, the test measures the promptness and sharpness of the body's response to insulin administered by vein. An insulin which has been freed of its hyperglycemic-glycogenolytic factor, "glucagon," is used. A single dose of 3 units of this insulin is given by vein in the fasting state. Venous glucose levels are determined in the fasting state and at 2, 4, and 6 minutes after the administration of insulin. The normal individual exhibits within the six-minute period a fall in blood glucose of 19 per cent, with a differential of ±7 per cent (Fig. 1). When the fasting level in normal individuals happens to be unusually low, there usually occurs a primary rise rather than the anticipated fall in blood glucose, a finding which can lead to false interpretation of the test. These criteria have been established by a study of over 600 tests to date.

△ Replicate determinations made on the same blood samples fell within the range of error incidental to the methodology employed, i.e., a standard deviation of from 5 to 5.3 mg per 100 ml of whole blood. To favor conservatism in the interpretation of the intra-individual variations found in this study, no variation was deemed to be significant unless it exceeded 8 mg per 100 ml of blood (an arbitrary increase of 66 per cent above the error actually and repeatedly found in 10 aliquots on individual single specimens of blood). Chi Square (goodness of fit) tests carried out on these aliquot series yielded a P (probability) of 0.99.

PROCEDURE

The Somogyi-Nelson macro method[7] for true blood glucose was employed in all glucose determinations (using 1 ml of fluoridized whole blood).* A number of these tests were performed in complete duplicate on individual samples of whole blood until such time as the range of error incidental to the method had been proved with certainty. Thereafter, duplicate readings were made only on filtrates; when these were not identical or not within the range of error, mean values were recorded as the accepted readings. In several cases the reducing substance was verified as being true glucose by parallel quantitative fermentation procedure.

A single team of two persons carried through all of the 3000 blood glucose determinations involved in this study.

To obviate repeated venipuncture, a 20-gauge needle was inserted into an antecubital vein and fixed in place by adhesive tape. A slow infusion of physiologic saline solution was instituted in order to keep the needle patent between blood samplings. The volume of saline infused was kept at a minimum and from beginning to end of the procedure rarely exceeded 60 ml. To assure against error incidental to venous dilution, hematocrit determinations were made on successive samples in random cases.

A tourniquet was used only at the time of insertion of the needle into the vein, the blood collected on this occasion always being discarded. All venous determinations were made on freely flowing blood coursing through unobstructed venous channels. The blood was collected in dry 2-cc Luer syringes. Eight minutes were allowed to elapse after the insertion of the needle before any sampling

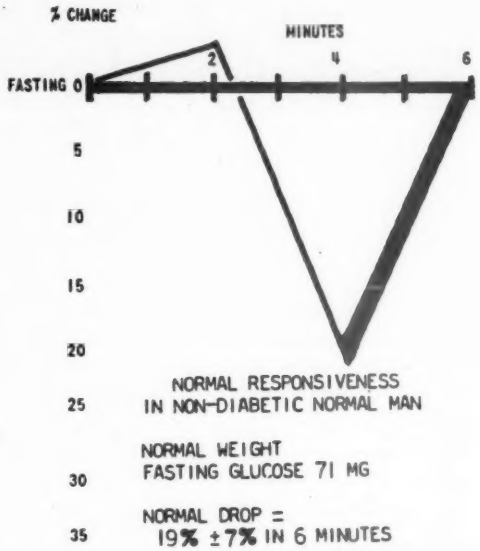

Fig. 1. Normal six-minute responsiveness test to 3 units of glucagon-free insulin by vein.

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was made. During this period, the individual's attention was distracted by conversation and efforts at reassurance. Continuous observation was made for any symptom suggesting an "epinephrine" effect. Blood pressure and pulse were followed in the opposite extremity throughout the entire procedure. Any evidence of adrenal medullary effect disqualified the individual from being included in the series.

After an eight-minute period of quiet recumbency, blood samples were taken at the zero point, at two minutes, at four minutes, and in many subjects also at six minutes. Occasionally, the two-minute sampling was carried out for as long as 30 or 60 minutes.

FINDINGS

In a determination of blood glucose level made two minutes after an initial reading, 46 per cent of 100 individuals studied showed a spontaneous significant variation from the original reading (Table I). Within another two minutes after the original determination (at four minutes) the number showing significant variation had increased to 74 per cent.

* All pipettes were carefully checked for correct calibration by the mercury technique. The Evelyn photoelectric colorimeter was used as standard in the colorimetric determinations. After development of the color, the Folin tubes were permitted to stand for 80 minutes, the time required for the establishment of a fixed plateau of color.[19] Duplicate readings made 12 hours later showed no significant change.

TABLE I

Consecutive Postabsorptive Blood Glucose Readings in 100 Unselected Individuals (Normal, Nondiabetic Obese and Diabetic) at Two-Minute Intervals

(True Macro Blood Glucose [Somogyi-Nelson])

Case No.	At zero time	2 min later	4 min later	6 min later
524	95	93 (2) NS*	95 (2) NS	91 (4) NS
523	114	123 (9)	107 (16)	123 (16)
521	107	103 (4) NS	93 (14)	107 (14)
502	181	187 (6) NS	162 (25)	167 (25)
499	136	136 (0)	132 (4) NS	122 (14)
484	122	117 (5) NS	147 (30)	
479	134	144 (10)	144 (10)	
517	148	123 (25)	123 (25)	120 (28)
511	129	117 (12)	124 (12)	138 (21)
503	161	152 (9)	107 (54)	101 (60)
485	199	206 (7) NS	174 (32)	
472	134	103 (31)	134 (31)	
468	101	146 (45)	152 (51)	
463	82	105 (23)	93 (23)	
458	134	112 (22)	134 (22)	
455	157	132 (25)	132 (25)	
537	124	124 (0)	114 (10)	118 (10)
547	112	108 (4) NS	101 (11)	108 (11)
14	146	146 (0)	143 (3) NS	143 (3) NS
15	137	146 (9)	143 (9)	148 (11)
12	174	169 (5) NS	171 (5) NS	174 (5) NS
11	120	114 (6) NS	126 (12)	108 (18)
10	89	79 (10)	79 (10)	79 (10)
9	60	50 (10)	50 (10)	50 (10)
505	99	95 (4) NS	105 (10)	109 (14)
1	50	47 (3) NS	47 (3) NS	49 (3) NS
535	70	66 (4) NS	67 (4) NS	70 (4) NS
534	245	234 (11)	230 (15)	234 (15)
533	137	146 (9)	149 (12)	137 (12)
530	68	58 (10)	54 (14)	81 (27)
528	95	103 (8) NS	79 (24)	79 (24)
464	168	146 (22)	157 (22)	
461	174	152 (22)	152 (22)	
460	77	69 (8) NS	73 (8) NS	
457	168	162 (6) NS	192 (30)	
453	132	152 (20)	141 (20)	
451	168	198 (30)	178 (30)	
447	244	244 (0)	244 (0)	
516	138	136 (2) NS	123 (15)	106 (32)
481	71	64 (7) NS	85 (21)	82 (21)
497	82	67 (15)	57 (25)	51 (31)
496	60	60 (0)	67 (7) NS	82 (22)
477	71	78 (7) NS	74 (7) NS	
475	82	74 (8) NS	114 (40)	
450	54	54 (0)	54 (0)	
448	67	71 (4) NS	74 (7) NS	
17	73	75 (2) NS	80 (7) NS	77 (7) NS
16	75	63 (12)	66 (12)	75 (12)
529	77	72 (5) NS	68 (9)	72 (9)
513	81	70 (11)	67 (14)	68 (14)
503	77	62 (15)	67 (15)	
495	88	88 (0)	73 (15)	
462	74	74 (0)	64 (10)	
449	82	82 (0)	82 (0)	
600	132	74 (58)	105 (58)	97 (58)
601	69	67 (2) NS	45 (24)	49 (24)
602	75	66 (9)	65 (10)	60 (15)
603	61	57 (4) NS	50 (11)	50 (11)
604	76	62 (14)	47 (29)	56 (29)
605	74	105 (31)	97 (31)	85 (31)
606	71	64 (7) NS	82 (18)	64 (18)
607	80	69 (11)	66 (14)	66 (14)
608	51	54 (3) NS	49 (5) NS	49 (5) NS
609	107	82 (25)	57 (50)	61 (50)
610	71	60 (11)	71 (11)	71 (11)
527	121	108 (7) NS	126 (18)	121 (18)
526	96	84 (12)	86 (12)	92 (12)
525	132	132 (0)	130 (2) NS	126 (6) NS
522	185	166 (19)	160 (15)	166 (15)
520	96	107 (11)	90 (17)	98 (17)
519	68	64 (4) NS	68 (4) NS	78 (14)
515	127	119 (8) NS	119 (8) NS	110 (17)
514	204	185 (19)	188 (19)	207 (22)
512	228	224 (4) NS	206 (22)	206 (22)
509	216	209 (7) NS	216 (7) NS	203 (13)
508	146	129 (17)	102 (44)	94 (52)
507	227	223 (4) NS	258 (35)	227 (35)
504	111	111 (0)	101 (10)	115 (14)
501	196	190 (6) NS	196 (6) NS	177 (19)
500	122	85 (37)	105 (37)	89 (37)
498	105	97 (8) NS	97 (8) NS	71 (34)
493	109	105 (4) NS	109 (4) NS	
491	122	146 (24)	132 (24)	146 (24)
490	192	179 (13)	...	192 (13)
489	157	173 (16)	152 (21)	146 (27)
488	136	136 (0)	132 (4) NS	132 (4) NS
487	67	74 (7) NS	82 (15)	67 (15)
486	163	168 (5) NS	174 (11)	
483	127	122 (5) NS	114 (13)	127 (13)
482	152	179 (27)	157 (27)	
480	116	120 (4) NS	107 (13)	
478	103	107 (4) NS	87 (20)	
476	109	118 (9)	118 (9)	
474	204	241 (37)	218 (37)	
473	179	179 (0)	185 (6) NS	
471	183	174 (9)	160 (23)	
470	109	93 (16)	127 (34)	
469	146	146 (0)	141 (5) NS	
467	89	101 (12)	114 (25)	
465	192	192 (0)	192 (0)	

In parentheses, maximum variation up to that time.
* NS = Not significant.

Two minutes later (at six minutes) 81 per cent of the persons had exhibited significant variation from reading to reading within this period. The variation ranged from 9 mg to as high as 60 mg per 100 ml of whole blood* with a mean variation of 22.2 mg (over four times the actual error found incidental to the method).

There was no fixed periodicity to the fluctuations, which always tended to be totally irregular in rhythm (aperiodic). Repetition of the testing procedure in given individuals at different times of the postabsorptive state showed the undulations to be consistently present at any and at all times throughout this period.

The variations found in successive readings in individuals usually extended far beyond the standard error inherent in the method. Their existence as a phenomenon of rapidly changing blood glucose level could accordingly, in no sense stand as an equivocal observation.

* Readings showing variations of 50 mg or more per 100 ml of blood appeared to be so fantastic that repetitions of such tests in these individuals on other days were carried out. The high degree of variation was reproducible and presumably represented a labile state of blood glucose characteristic of these individuals. This is especially true of the "labile diabetic."

FINDINGS IN DOGS

The consistency of the finding of spontaneous postabsorptive venous blood glucose fluctuation in man prompted a repetition of the investigative procedure in normal dogs at various times of the postabsorptive state. A total of 20 sets of blood glucose readings were made at short interval in dogs under pentobarbital anesthesia. The glucose determinations in each instance were carried out for no less than ten minutes of time. In all of the dogs, however, simultaneous arterial and venous readings were made (usually from a single extremity). Most of the sampling in dogs was done at one-minute intervals and in several animals at 15-second intervals (Fig. 2).

In the one- or two-minute blood samplings for glucose, all of the dogs showed the same type of venous glucose undulation commonly found in humans (Figs. 2 and 3). When, however, in dogs, the time interval between readings was reduced to 15 seconds, there were exhibited markedly accentuated oscillations* in blood glucose in both directions (Fig. 4). This increased excursion at 15-second interval was found not only in venous but also in the arterial blood.

A most interesting finding was that a rise in arterial glucose level was practically always associated with a fall in glucose on the venous side of the extremity.† Correction for the blood circulation time from the arterial to the venous side (thereby establish ng the venous lag) served to confirm this reciprocal correlation between the arterial and the venous undulations and oscillations (Fig. 5).

The usual finding in the dog of a reciprocal relationship between the arterial and the venous fluctuations prompted further investigation in man. Femoral arterial and venous blood from a single extremity in man exhibited the presence of the same reciprocal phenomenon (Fig. 6).

When in the dog the 15-second venous readings were plotted and every fourth reading was bridged so as to indicate blood glucose trends on a minute-to-minute basis, there were reproduced the same type of postabsorptive venous undulations characteristically found not only in all of the dogs studied but also in the human subjects (Fig. 7). Presumably, the long undulations exhibited in both species are made up of aggregates of successive sharp precipitous oscillations, the flings of which in both directions usually require about 30 seconds for the completion of both up and down phases.

The one-minute and two-minute variations in the dog were usually of smaller amplitude than those observed in humans, the undulations from crest to trough varying from 7 to slightly over 20 mg per 100 ml of blood. In contrast to their sharp component oscillations, these long undulations exhibited wave-lengths ranging from two to seven minutes (Fig. 7).

Simultaneous arterial readings at one-minute and at 15-second intervals on blood from the brachial arteries of both forelegs of a dog were taken. The gross undulations were found to be

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* In this study of fluctuations in blood glucose, a precise etymological differentiation has been made between the terms "undulation" and "oscillation." Webster's *Unabridged Dictionary* defines an oscillation as "a single swing from one extreme limit to the other" —"a change back and forth or above and below a mean value." An undulation, on the other hand, connotes a wave-like progression with crests and hollows, a much smoother phenomenon with multiple points of rise and fall. From the geometrical viewpoint, Webster defines an undulation as "a point of a plane curve counting as four (or any higher even number of) intersections of the curve with its tangent so that the tangent does not cross the curve."

In this communication, the undulation with its extended wave-length is deemed to be made up of an aggregate of multiple single oscillatory swings in close succession.

† The time relationship between the arterial and the venous readings was established with stop-watch precision on freely flowing blood, with due attention being paid to correction for venous lag by determination of circulation time from point to point by fluorescine. A sustained intravascular pressure was maintained throughout the experiment. In only one instance was a cannula tied into the vein. The findings in this animal were discarded as possibly representing readings on samples which may in part have been made up of stagnated venous blood and which, accordingly, might have been out of rhythm with the other glucose readings in this animal.

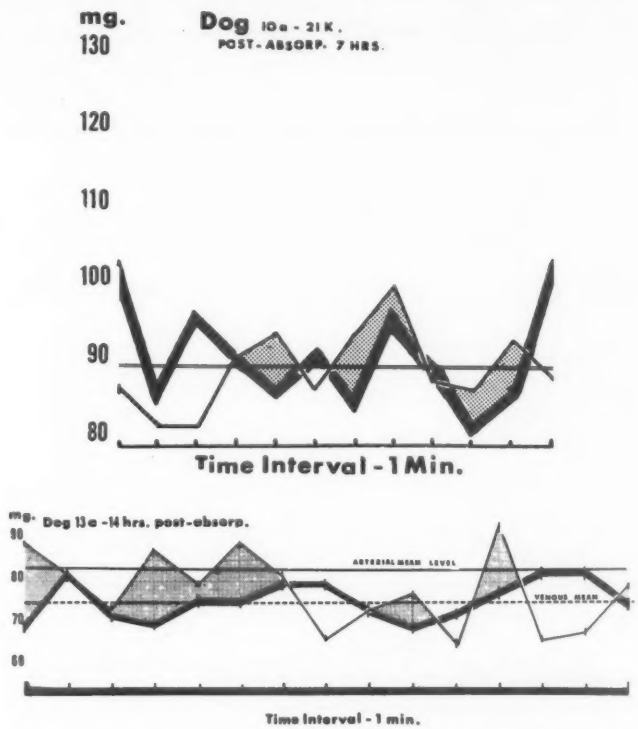

Fig. 2. Simultaneous arterial and venous true blood glucose undulations in normal dogs. Fine line represents arterial glucose curve; heavy line, venous glucose curve; shaded areas, arteriovenous difference.

parallel in both. The 15-second fluctuations showed some divergence, a finding which is readily explainable by the moment-to-moment differences in the local tissue demands for glucose and by the irregular and apparently capricious transfer of glucose across molecular or cellular barriers.

To establish the fact that the oscillations and undulations found in arterial blood emanate, in the main, from the liver, blood samples were taken at one-minute and at 15-second intervals from the hepatic vein and simultaneously from the femoral artery and vein of an extremity. Correction was made for the blood circulation time between the hepatic vein and the femoral artery, as well as between the femoral artery and vein of the extremity. For these determinations, fluorescine under a Wood lamp was employed. The procedure was carried out under pentobarbital anesthesia, with direct exposure of the hepatic vein in a heavily ergotaminized dog under oxygen insufflation in a closed system. When these glucose readings were plotted in parallel, there appeared an unmistakable identity between the fluctuations emanating from the liver and those found in blood from the femoral artery (Fig. 8). The mean glucose level in femoral arterial blood was, as might have been anticipated, definitely lower than that in blood emanating from the liver, the mean level of 19 readings from each source being, respectively, 78.3 (hepatic) and 76.2 mg (femoral artery) per 100 ml of blood. The experiment was repeated with similar findings in a second animal.

On three occasions it was demonstrated that ligation of the abdominal aorta and vena cava

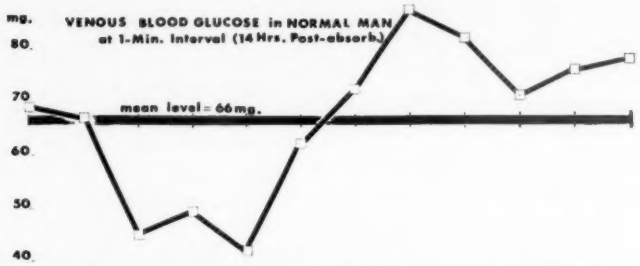

Fig. 3. Normal blood glucose undulations in normal male medical student, 14 hours postabsorptive.

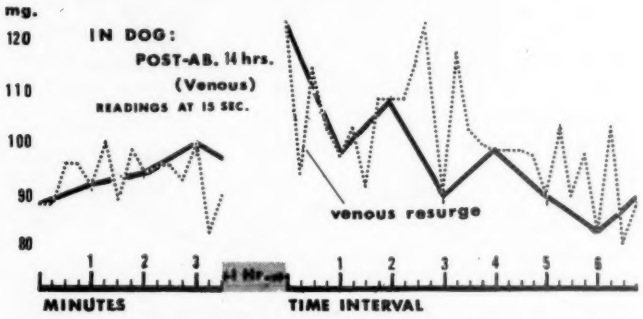

Fig. 4. Venous oscillations and undulations in normal dog, 14 hours post-absorptive. Glucose readings at 15-second interval. Note the rapid venous rebound.

together with hepatectomy resulted in loss of peripheral arterial undulations (Fig. 9). This finding supports the fact that the arterial fluctuations originate in the liver.

DISCUSSION

Teleologically, the consistent and invariable presence of wide arterial and venous glucose oscillations throughout the entire *postabsorptive* period both in man and in the dog would suggest that their existence may very possibly serve a physiologic purpose. It is an accepted fact that during the *absorptive* state glucose in the arterial blood supply to the pancreas acts as a trigger mechanism to insulin production by that organ.[8] In a broader sense, and on a longer time-range, ingested glucose in adequate amounts also leads to a unit for unit increased functional capacity of insulin, an increased sensitivity to insulin and hence greater effectiveness of the hormone.[9–14]

It is reasonable to conjecture that glucose, so consistently released from the liver into the arterial stream in transient spurts throughout the entire postabsorptive period, may serve the same physiologic purpose as does ingested glucose during absorption, that of activating insulin production as well as its function. It is now well recognized that insulin activity takes place not only during the state of absorption of ingested food but also throughout the period of postabsorption. This fact calls for some thought as to how such insulin function is provoked during the long period of postabsorption when no ingested glucose is entering the portal circulation.

Promptly following each arterial spurt of glycemia, it was noted both in dogs and in man that there occurs a decided fall in the venous glucose level (Fig. 5). We suggest that the descending limb of each of these venous oscillations represents a sharp but brief episode of insulin effect which registers itself peripherally as a sharp increase in the gradient of glucose

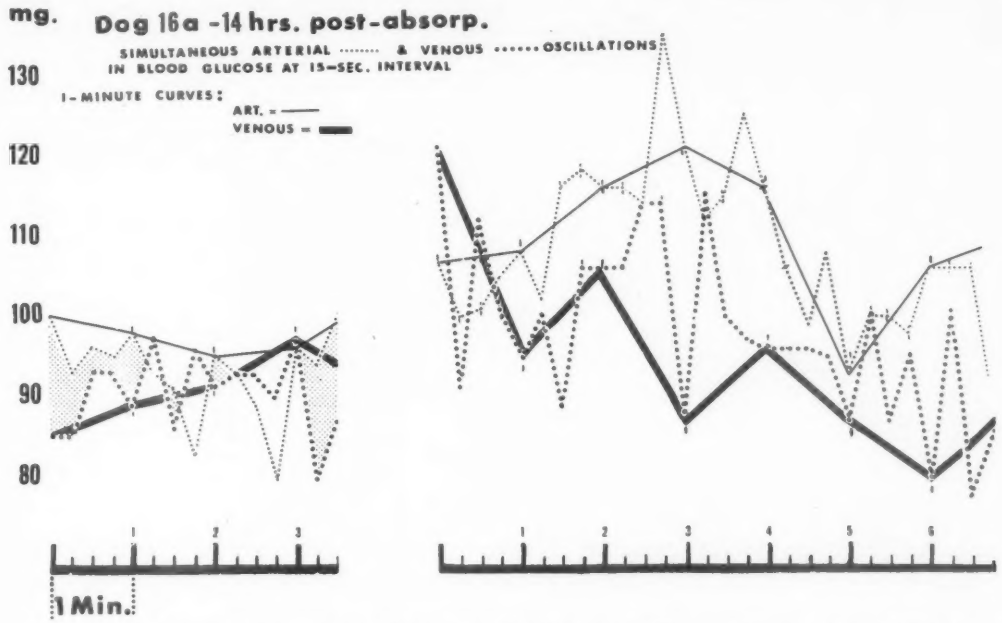

Fig. 5. Spontaneous simultaneous arterial and venous blood glucose readings at 15-second interyals in an intact normal dog. Note intense excursion from reading to reading. When these readings are replotted so as to establish a curve on a minute-to-minute basis, there is reproduced the pattern of undulations similar to those found during postabsorption in 100 humans and in all of the dogs studied. The break in the curves represents an interval of one hour. A resumption of 15-second readings shows even more pronounced oscillations. The explanation for this accentuation we do not have.

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transfer across cellular or molecular barriers. It is further proposed that the excitant of each such phase of insulin action may be the brief *arterial* glycemia exhibited immediately before the respective *venous* fall. A study of the blood circulation time in one extremity, determining the time for the blood to travel from the arterial to the venous side of that extremity,* seems to verify the existence of a direct temporal correlation between the arterial rises and the venous falls in the respective blood glucose oscillations.

The Speed of Peripheral Action of Insulin

The question would naturally arise as to how the venous level of blood glucose could possibly change so sharply as is suggested by the 15-second variations, if the descending phase of each venous oscillation truly represents a physicochemical transfer of glucose across cellular or molecular spacial barriers. Part of the answer to this question is suggested by the sharpness and massiveness of the descent in venous blood glucose incidental to a very small dose of glucagon-free insulin administered by vein. In fact, the dose may be so small as to suggest that this substance must exercise a "catalytic" rather than only a stoichiometric mass effect (1 to 3 units, or less than half the amount of insulin used in conventional insulin sensitivity tests). Normally (Fig. 10), a sharp fall in the venous glucose level usually occurs well within one minute and often within 15 seconds of time after the administration of glucagon-free insulin by vein or by artery. One may add to this clean-cut observation the fact that when normal rat diaphragm[15] is even momentarily dipped into a buffered solution of insulin, the insulin promptly becomes

* Using fluorescine under a Wood lamp, the circulation time from the arterial inflow to the venous outflow in an extremity was found to vary in different animals from 4.5 to 10 seconds.

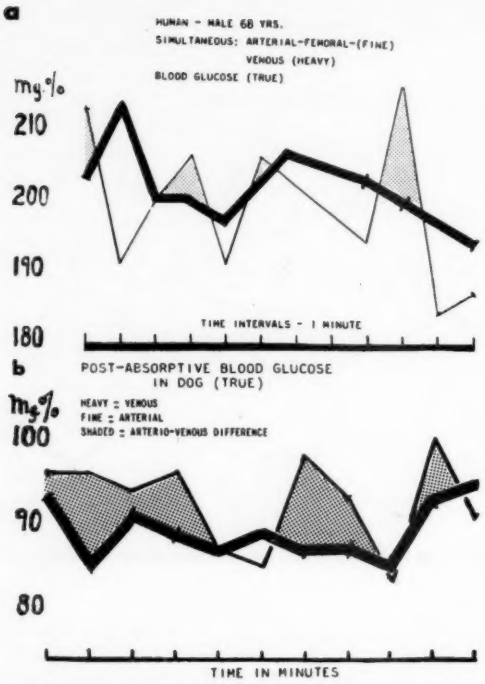

Fig. 6. Comparison between the spontaneous post-absorptive glucose undulations found in man (a) and in the dog (b).

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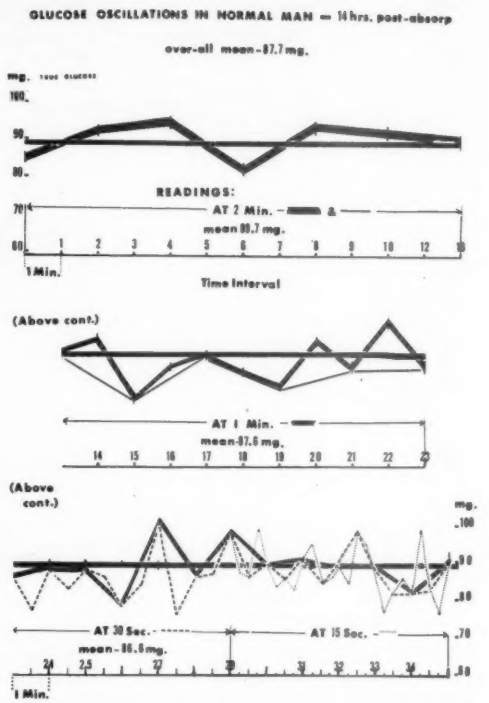

Fig. 7. Breakdown into their component oscillations of spontaneous blood-glucose venous undulations found in man.

inextricably bound to the muscle tissue, presumably by an instantaneous physicochemical action. The firm fixation of insulin to the tissue immediately becomes so positive that the attachment subsequently resists all efforts to break it up by vigorous washing of the tissue with plain buffer solution.[16] These two facts, each reflecting the rapidity of the speed of action of insulin, suggest that *in vivo* insulin function at the tissue level is not the sluggish process usually envisioned but is registered as a very rapidly moving mechanism of mobilization of glucose across barriers. In all probability, the initiation of such insulin function (or the latent period of the hormone, as it were, at the tissue level) is limited only by the circulation time for the insulin to reach its peripheral target in the tissues. *In vivo*, the transfer of glucose across barriers at this point is then so prompt, and, at the same time, the bulk of the transfer is so widely and so massively distributed over the body's musculature, that the over-all effect of the hormone on the venous level of glucose would appear to be just as massive as the insulin has been prompt in its fixation to the tissues. The extent of fall in venous glucose would seem to hinge directly on the bulk of peripheral tissue which has been subjected to the fixation of insulin and would, accordingly, be conditioned by the state of glucose transfer at that particular point. The fall in venous glucose after the injection of even a very small dose of glucagon-free insulin into the blood stream is so prompt and massive as to suggest that smaller pulsatile physiologic releases of the hormone in brief spurts could accomplish the very same "catalytic" effect of an intermittent transfer of glucose across the barriers.

The Venous Resurgence of Glucose

The sharp "down-and-up" oscillations in venous glucose can be discerned at any and at

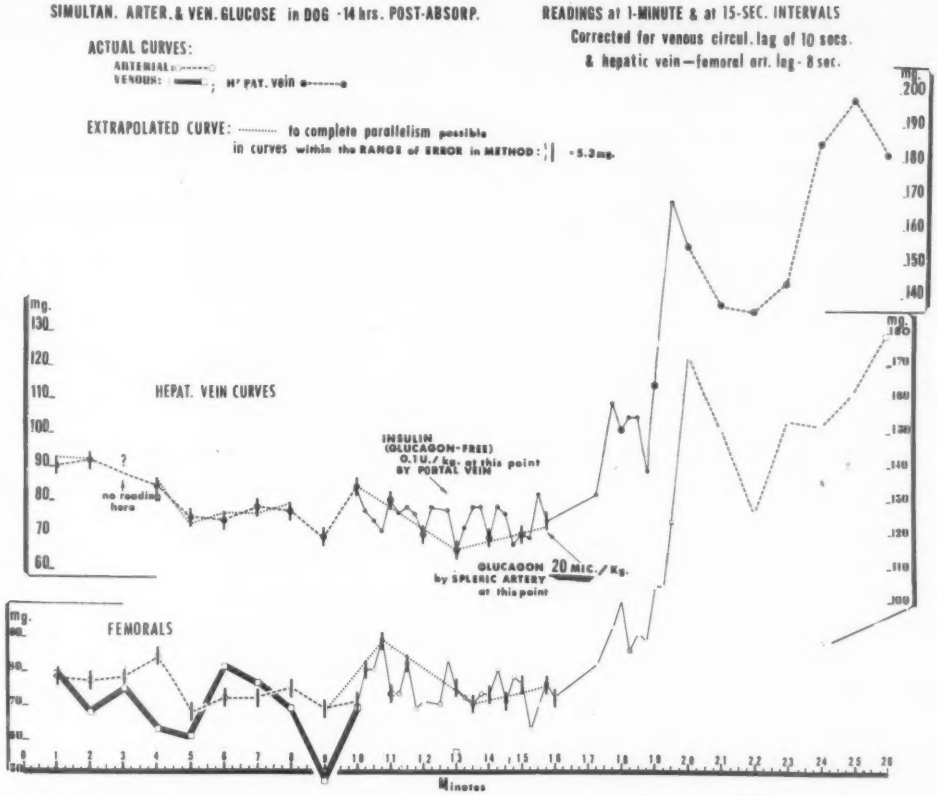
SIMULTAN. ARTER. & VEN. GLUCOSE in DOG · 14 hrs. POST-ABSORP.
READINGS at 1-MINUTE & at 15-SEC. INTERVALS
Corrected for venous circul. lag of 10 secs.
& hepatic vein—femoral art. lag - 8 sec.
ACTUAL CURVES:
ARTERIAL:
VENOUS:
H' PAT. vein
EXTRAPOLATED CURVE: ..... to complete parallelism possible
in curves within the RANGE of ERROR in METHOD: -5.2mg.
HEPAT. VEIN CURVES
INSULIN (GLUCAGON-FREE) 0.1 U./kg. at this point BY PORTAL VEIN
no reading here
GLUCAGON 20 MIC./Kg. by SPLENIC ARTERY at this point
FEMORALS
Minutes

Fig. 8 Identity of peripheral arterial blood glucose (true) undulations with those exhibited in hepatic vein.

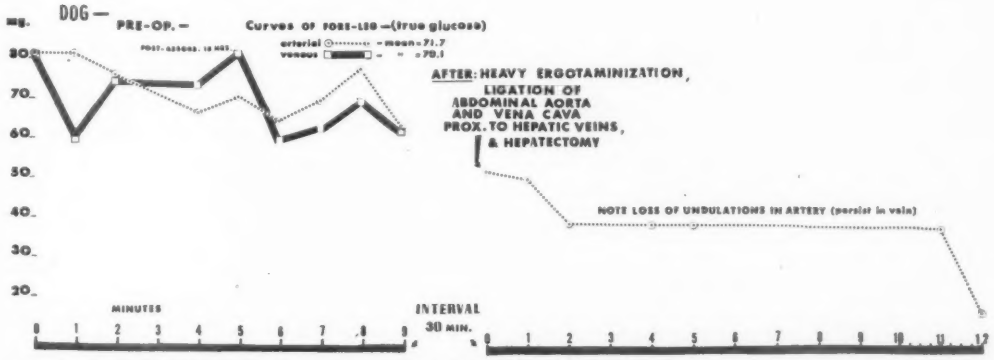
DOG —
PRE-OP. —
Curves of POST-LIG.—(true glucose)
arterial
venous
AFTER: HEAVY ERGOTAMINIZATION, LIGATION OF ABDOMINAL AORTA AND VENA CAVA PROX. TO HEPATIC VEINS, & HEPATECTOMY
NOTE LOSS OF UNDULATIONS IN ARTERY (persist in vein)
MINUTES
INTERVAL 30 MIN.

Fig. 9. Loss of peripheral arterial undulations by ligation of abdominal aorta and vena cava proximal to liver, followed by total hepatectomy. Animal previously ergotaminized (0.5 mg dihydroergotamine by vein) before operative procedure. It had previously and repeatedly been demonstrated that ergotamine has no influence whatsoever on the arterial undulations found during the control period.

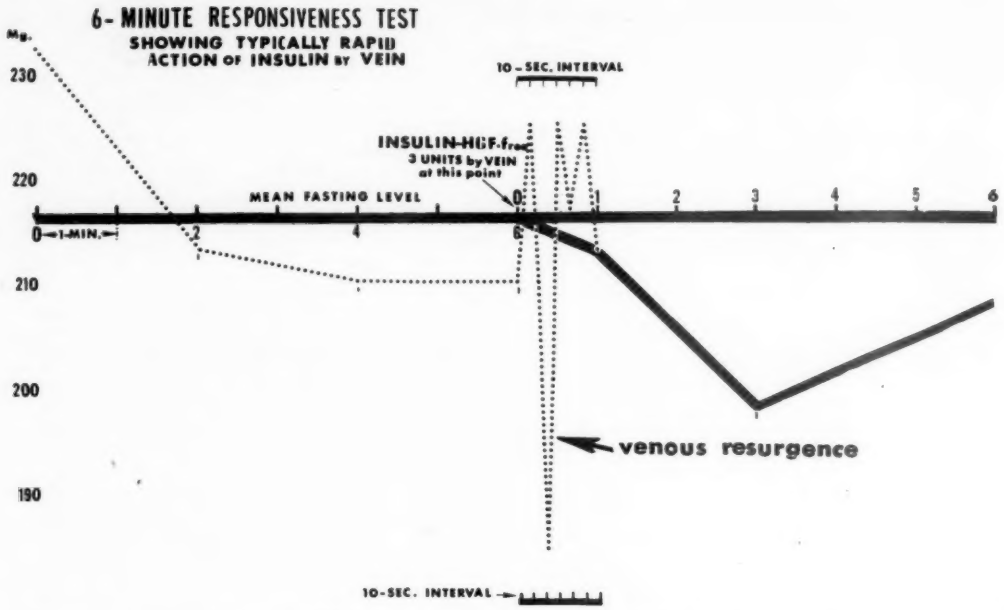

Fig. 10. Breakdown of typical six-minute insulin responsiveness test into its component oscillations. Note speed of action of insulin, a precipitous fall in venous glucose within 20 seconds. There is also a prompt rebound (venous resurgence of glucose).

all times of the postabsorptive period, if readings are made at 15-second intervals. They would seem to represent at the local tissue level a to-and-fro tide of glucose across barriers, there possibly being retained behind these barriers only such glucose as has actually been engaged or captivated by phosphorylation by the intracellular enzyme systems. The prompt rise or rebound in venous glucose immediately following each short precipitous fall in the glucose content of venous blood from an extremity would seem to represent glucose returning into the venous channels from behind the barriers, perhaps that glucose which has not undergone esterification. This suggestion of glucose resurgence is in complete consonance with the theory propounded by Levine and others, that all "transferred" glucose is not necessarily phosphorylated.[17,18] Also in keeping with this theory is our own finding that the mean value of all of the venous oscillatory deflections is practically constant, save that over an extended period of minutes or hours this mean level gradually but slowly becomes lower and lower. This falling over-all mean level of glucose presumably reflects such glucose as has been captivated behind the barriers by phosphorylative esterification.

To insulin at the peripheral level has been ascribed the function of a unidirectional transfer of glucose across barriers. The venous resurgence of glucose would rather suggest the existence of a bidirectional transfer, the mechanism of which is still problematical. The validity of this entire proposition of venous resurgence must, of course, await confirmation by isotopic tagged glucose studies. It is obvious, however, that during postabsorption most of the surging bulk of glucose penetrating the barriers promptly returns to the local venous channels, thereby creating within a matter of a few seconds the sharp reversal in glucose content registered by the ascending limbs of the venous oscillations (Figs. 4 and 10). The rapidity of the change from a fall to a rise

in glucose is too great to permit of the concept that such rising glucose is of central (liver) origin. The length of the blood circulation time between the liver and the peripheral point where the venous change is being exhibited would preclude any such possibility.

The mechanism of the normally occurring venous oscillations would be most difficult to explain if one were not to accept the principle that the transfer of glucose across physicochemical barriers is commonly a phenomenon of bidirectional exchange rather than the generally accepted one of massive uncompensated mobilization entirely in the direction of the tissues. In the absence of muscular contraction (under anesthesia), venous resurgence rather than glucose captivity behind the barriers seems to be the normally dominant mechanism during postabsorption.

The Effect of Extrinsic Insulin on Fluctuations

A very small dose of glucagon-free insulin administered by vein from without shatters the spontaneous homeostatic smoothness of the normal to-and-fro venous tide of glucose both in man and in the dog. The effect of such unnatural intrusion of insulin from without is the prompt creation of "forced oscillations"* with increased amplitude of swing in both directions (Fig. 10). When the dose of insulin is further increased so as to become massive, the normal bidirectional flow of glucose gives way to a steady unidirectional tide of glucose across the barriers with immediate captivation (Fig. 11). There occurs a deficiency of glucose on the side of the blood stream, with ultimate insulin reaction and reactive adrenal medullary over-correction.

The pulsatile character of the oscillations, moreover, would also suggest that insulin function during the postabsorptive period is never normally a linear effect on blood glucose between two points of time but is always a fluctuant phenomenon. A linear descent in glucose between two substantially spaced points of time, when it does occur, represents an unphysiologic state such as is induced by the intrusion into the picture of an unphysiologic dose of insulin from without. A massive dose of insulin by vein converts the normal to-and-fro glucose transfer into a precipitous unidirectional flooding across the barriers in the direction of the tissues, with the prompt production of an insulin reaction (Fig. 11).

The Origin of Arterial Glucose Fluctuations

Arterial undulations and oscillations apparently have an origin entirely different from the venous ones. They are essentially one and the same throughout the entire arterial system and are definitely identifiable with glucose fluctuations found in hepatic vein blood emanating from the liver. They are released irregularly[19] but in rapid succession from the liver in what seems to be a pulsatile manner.† The same undulations are to be picked up in the arteries of all four extremities. At their point of emanation in the hepatic veins they are, as would be anticipated, of higher glucose value than at the peripheral arterial levels. Presumably, there is a considerable loss of glucose in the passage of the blood through the heart and pulmonary circuits. The aperiodicity and the irregularity in magnitude of these fluctuations make possible their identification at peripheral arterial points when, in the process of blood-sampling, exact correction is made for the circulation time between the hepatic vein and the peripheral artery in question. In marked contrast to the arterial fluctuations, the venous glucose oscillations and undulations at the periphery are probably never at any

* Forced oscillations are "those of a body which can perform free oscillations" (the normal) "but which is subjected to a periodic force" (Webster).

† Bondy[19] found similar fluctuations in the hepatic veins of humans. These were rapid, irregular, and totally unpredictable, representing actual variations from moment to moment in the rate of production of glucose by the liver. He utilized hepatic vein catheterizations in humans, a setting of experimental circumstances which would be entirely different from those encountered on direct needling of the veins in dogs under anesthesia. Accurate timing of the peripheral manifestation of these same fluctuations would seem to have been impossible by a catheter technique.

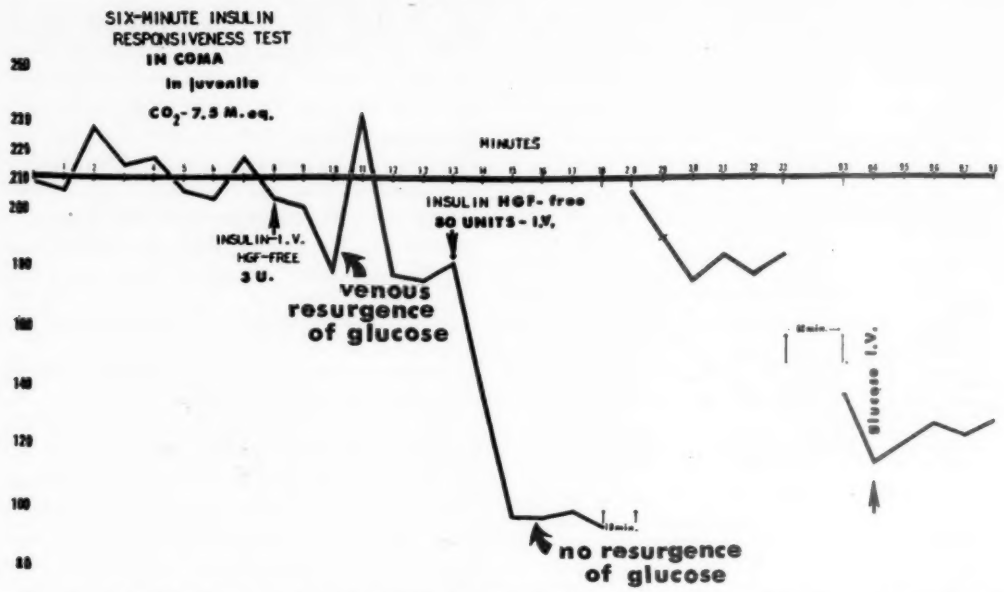

Fig. 11. Juvenile diabetic deep in ketotic coma but still surprisingly responsive to a small dose of glucagon-free insulin. Note the prompt venous resurgence, probably glucose which has crossed the barrier without being phosphorylated. Note the prompt precipitous fall in venous glucose after a massive dose of glucagon-free insulin administered by vein six minutes later—no venous resurgence. Transferred glucose was probably retained by the tissues. The patient recovered from coma without further administration of insulin. The reading at 28 minutes probably represents a temporary adrenal medullary countereffect which ultimately gives way to normal glucose level.

one time, except by accident, identical in two extremities. As would be anticipated, they vary at each peripheral point directly with the bulk of the tissue mass under the influence of the insulin fixed in the tissues at that point, as well as with the extent to which glucose resurgence is taking place from behind the barriers at that point.

Homeostasis and the Tissue Utilization of Glucose

In a given extremity, during postabsorption, the mean glucose level of the arterial oscillations and undulations tends to come close to or even to equal the mean level of the venous fluctuations (Fig. 2). In spite of the marked excursions in both arterial and venous blood, the actual net total fall in mean glucose on both sides of the circulation is relatively small, even after many minutes of such seeming caprice. The lively up-and-down fluctuation would appear to be linked with a normal homeostatic mechanism by which the body maintains an over-all constancy in blood glucose level. A facile redistribution of glucose into and out of the blood stream would seem to create the purposed homeostasis.

One is driven to think of the momentary arteriovenous (A-V) differences spotted in the simultaneous arterial and venous readings as not necessarily representing a true measure of the peripheral utilization of glucose. They are merely momentary snap-shots of transfer conditions in glucose only as these happen to be registered *at such specific instants* of time. During postabsorption, the A-V differences vary strikingly from minute to minute as a result of the venous resurgence of glucose. The spot-picture of an A-V difference, accordingly, cannot possibly represent the actual tissue utilization of glucose. It is merely a momentary phase of such (possible) utilization. By the same token, during postabsorption no

one or two determinations of A-V difference spaced at half-hour or longer intervals can possibly reflect what is happening in an extremity or in the body as a whole in respect to the "utilization" of glucose. Too much fluctuation is actually taking place between any two such widely spaced points of time to warrant any such generalized concept.

SUMMARY

The postabsorptive blood glucose level is practically never static for longer than a few moments at a time. It is a constantly changing phenomenon with sharp diphasic oscillations, each to-and-fro oscillation taking approximately 30 seconds, more or less, for its completion. The only realistic picture of a continuously moving function, which is obviously so dynamically active as is glucose exchange across barriers, would seem to be one represented by the concept of the motion-picture, an assembled run in rapid succession of a large number of single "snap-shots" of blood-glucose status.

Eighty-one per cent of 100 unselected humans in whom successive venous true-glucose determinations were made at two-minute intervals over a four- or a six-minute period, showed significant variation from reading to reading. The intraindividual mean significant variation among these successive readings was found to be 22.2 mg per 100 ml blood, which is over four times the *actual* error (5.3 mg per 100 ml) incidental to the methods employed.

When these venous glucose readings are plotted at two-minute intervals, they assume the form of smooth aperiodic undulations with wave-lengths of from two to seven minutes. Repeated break-down of these undulations at random into their component fluctuations (readings at 15-second intervals) shows each undulation to be made up of a succession of these two-phased oscillations. It is proposed that the sharp venous descent in each completed oscillation represents the momentary transfer of glucose across cellular or molecular barriers. Each precipitous descent is immediately followed by an equally sharp rebound in venous glucose, a finding which can reasonably be interpreted only as a resurgence of glucose back into the venous channels from behind the barriers. The speed of the rebound (when compared with the over-all circulation time) would preclude there being any central origin for this precipitous rise in venous glucose.

Even with careful correction for circulatory lag, the venous undulations and their component oscillations are identical at no two points throughout the entire venous system (except by accident). They are thought to vary in accordance with the tissue uptake and with the resurgence of glucose at each tissue point (with the peripheral function of insulin).

Similar aperiodic *arterial* undulations with component oscillations were found to arise in the liver. By contrast with the venous fluctuations, however, arterial undulations are identifiable as being uniform throughout the entire arterial system by careful circulatory timing.

During postabsorption (at rest), the mean glucose level of all arterial undulations and oscillations tends to equal rather precisely that of the fluctuations on the venous side. There is, however, a gradual descent of this mean level over the hours of postabsorption, the difference probably representing the net captivity of glucose by the tissues in phosphorylative esterification, the over-all deficit between the transfer across barriers and the venous resurgence of glucose.

The reciprocal relationship found to exist between arterial and venous glucose levels, with the maintenance of almost identical mean values for each, further suggests that the oscillatory activity characteristic of the postabsorptive period is one means by which the body maintains blood glucose homeostatically constant between its production by the liver and its transfer across cellular or molecular spacial barriers.

The phenomenon of insulin action in the periphery is far more rapid than has generally been appreciated. *In vivo*, the transfer of glucose across peripheral barriers takes place rather massively within a matter of seconds of time after exposure of the peripheral tissues to insulin. The total effect of insulin in this

respect would seem to be registered as the summation of a continuous succession of brief spurts of the hormone rather than the single precipitous dumping out into the blood stream of a reservoir content of the hormone. The over-all glucose-lowering effect of the hormone is, accordingly, under *normal* conditions not linear between two widely separated points of time, but is reflected as the ultimate mean of a constantly fluctuating blood glucose level. The same aperiodic principle applies to A-V difference in respect to the tissue "utilization" of glucose.

CONCLUSION

During the postabsorptive period, the blood glucose level is a constantly changing dynamic phenomenon with "ups and downs." Accordingly, a single fasting blood glucose determination can represent a spot picture of glucose status only at that particular instant. Fasting blood glucose level can be approximated, but even then only crudely: (1) by determining successive blood glucose readings at two-minute intervals, and (2) by considering the fasting level to be the mean of at least three or four such readings. A fairly representative fasting blood glucose level can be obtained by withdrawing blood steadily and slowly over three minutes in a well heparinized syringe, provided no tourniquet is used. The blood should be fluoridized and well shaken after withdrawal.

The consistent presence during postabsorption of short spurts of arterial glucose originating in the hepatic veins and identifiable throughout the entire arterial system would suggest that the fluctuations serve the physiologic purpose of (1) activating insulin function during this period, much as does ingested glucose during the period of absorption, (2) supplying a gradient of glucose at the tissue points to be engaged by such insulin as has been fixed at these points.

ACKNOWLEDGMENTS

The glucagon and glucagon-free insulin used in these studies were supplied by Eli Lilly and Co. through the courtesy of Drs. William R. Kirtley and Franklin B. Peck, Sr.

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Editorial

Antibiotics Plus?

Good medical practice is based upon the principle that the physician be well educated so that he can choose from the various therapeutic agents available those most suitable for the treatment of each patient. A corollary to this is the principle that mixtures of drugs may lead to "polypharmacy" and limit the free choice of the physician in the prescription of individual medicines for the best treatment of each patient. For example, the Council on Pharmacy and Chemistry of the American Medical Association states "the Council considers for evaluation drugs with a single active ingredient or extracts from a single source. Combinations or mixtures containing two or more active ingredients may receive consideration only if it is deemed desirable to present the Council's views regarding any such preparation for the information of the medical profession."[1] Finally, mixtures of drugs unless carefully studied may complicate evaluation of each of the drugs. It is for these reasons at least that many physicians look askance at the presently widely advertised mixtures of broad spectrum antibiotics in combination with vitamins.

Recently, several papers have appeared purporting to support the efficacy of such mixtures. In general, these papers imply, and in some cases state, that the antibiotic-vitamin combinations are more effective than the antibiotics alone. Scrutiny of the data does not support the allegation. One paper[2] states: "Because of the established experimental and clinical evidence that stress vitamins are of vital importance in reparative and recuperative efforts in persons subjected to serious surgical, traumatic, or infectious disease and trial, it is the author's impression that the antibiotic-vitamin combination represents a most valuable addition to the physician's armamentarium." Unfortunately, although this is the author's impression it should be remembered that his experimental and clinical evidence does not prove the point. In addition, the paper[2] offers no collateral controls; that is, the results of the treatment of patients with the antibiotic alone are not compared with the results of the antibiotic-vitamin mixture. From data such as these it is impossible to draw any but highly tentative surmises.

In another paper[3] the author discusses the use of tetracycline with vitamins in pediatric practice. Here again no controls are presented and it is stated "It is well established that, with the stress of infection, there is a need for increased vitamin intake." Unfortunately, there is little scientific evidence to justify such a statement. Tolerance to tetracycline combined with water-soluble vitamins has also been studied.[4] In this instance, it was concluded that the combination of water-soluble vitamins with tetracycline was clinically as effective as tetracycline alone. This presumably means that it is the authors' impression after comparing the vitamin-antibiotic treated cases with this previous experience. They note that a blindfold test of a large series of cases would be necessary before the impression could be established that untoward effects were less severe when vitamins were given with antibiotics than the antibiotics alone.

In support of the addition of vitamins to antibiotic preparations the report of the Committee on Therapeutic Nutrition of the National Research Council has been cited,[5] but no such combination was suggested. Furthermore, it was clearly stated in the introduction that the report was to be considered tentative pending further research results. The clinical and experimental effectiveness of vitamins in relation to antibiotics and to infection in general

has been ably reviewed.[6] Here it is clearly evident that little is known of the relation of vitamin nutrition to infection and other stress situations, nor is the relationship of antibiotic administration to vitamin metabolism at all clear. Finally and perhaps more important, vitamins are not the only nutrients required by sick (in addition to well) people. An adequate supply of calories, protein and certain minerals are needed as well. The availability of antibiotic-vitamin preparations is certainly no substitute for careful attention on the physician's part to the prescription of an adequate diet or the supplying in some other way of all needed nutrients to patients in the amounts required. In fact, it often cannot be accomplished, as the combination of vitamins and an antibiotic prevents altering the dose of the former without changing the latter.

Until it is an established fact that it is necessary to add vitamins to antibiotics and that the two in some way supplement each other, it seems both unnecessary and expensive for the patient to promote the use of these combined medications. Each is, of course, available separately and they can be given in any way a physician deems necessary on the basis of scientific evidence, his experience, and the patient's clinical condition. This would seem to be the best medical practice.

—CHARLES S. DAVIDSON, M.D.

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Coming

The March–April 1957 issue of THE AMERICAN JOURNAL OF CLINICAL NUTRITION will be of widespread interest. The entire issue will be devoted to a *Symposium on Nutrition and Behavior,* the proceedings of a meeting held in April 1956 at the School of Public Health, University of Minnesota, in cooperation with The National Vitamin Foundation. A large group of interesting observations are reported under the general headings of Impact of Diet on Behavior, Hunger and Appetite, Food Appraisal and Acceptance by Man, and Satiety and Weight Control. The unique program, arranged by Dr. Josef Brožek, will provide a permanent and useful record of active research in one of the most important—and neglected—spheres of human biology.

Reviews of Recent Books

Proceedings of Symposium on Nutritive Aspects of Preserved Food (SIK-Publication 115), Swedish Institute for Food Preservation Research, Göteberg, 1956, pp. 173, 30:-Sw. Fr.

There were 63 participants in this Symposium, representing eight countries, although most were from Sweden. The following are some of the salient points covered:

In spite of pasteurization, quite a number of people acquire diseases through milk. Extensive losses of valuable food have also taken place through milk bacteria. Gradually higher and higher temperatures are required in pasteurization to avoid all serious direct or indirect contamination by this channel. Sterilized milk may be considered completely safe, and in several countries milk sterilization is gradually becoming common practice.

With regard to toxicity in foods, it is pointed out that a substance in its free state may be toxic but harmless in combined form. As an example, the fluorine in the intestines of whales, seals, and several other animals, which constitute the basis of food of the Greenland Eskimos, is so high that it is far above the toxic levels; but apparently it is organically bound in such a way that no danger exists.

From enzymic model experiments it is known that a fat-protein complex (lipoprotein), for instance, is more readily attacked by the fat-splitting enzymes (lipases) than is the isolated fat. The proteinases seem to show the reverse reaction, being more active when the protein is free. These are basic facts which in the future will give a new approach to the technique of food preservation.

It was concluded from papers presented in this Symposium that the canning processes as a whole result in a remarkable degree of conservation of nutrients, provided reasonable precautions are taken by the canner. Delays in handling the raw materials must be avoided; the methods used in blanching vegetables must be closely controlled, so as to avoid the extraction and loss of water-soluble vitamins at this stage; and excessive sterilization processes must not be used, if the full thiamine content is to be retained. B. SURE

A Symposium on Amino Acid Metabolism, edited by W. D. McElroy and H. Bentley Glass, The John Hopkins Press, Baltimore, 1955, pp. 1048, $12.50.

Roughly one-fourth of the 58 papers comprising the symposium deal with general aspects of amino acid metabolism, the remainder with specific amino acids. The contributions consist of general reviews up to 50 pages in length and of shorter papers describing features of the metabolism of individual amino acids. The result is one of the most comprehensive presentations of this rapidly evolving field to be found anywhere.

Presentations that the writer found of special interest included the discussions of amino acid oxidases, decarboxylations, and transaminations by Meister and the extensive review of transport of amino acids into cells by Christensen. Striking progress in the experimental study of protein formation by a number of contributors are of fundamental significance, especially to those concerned with nutrition. These reports include descriptions of the synthesis of three enzyme systems by disrupted staphylococci in the presence of ATP, hexose diphosphate, an amino acid mixture, and RNA and DNA or their equivalent as purines and pyrimidines. Deserving mention also, is the hypothesis of Dubnoff, who ascribes to vitamin B_{12} an ability to induce activity in enzymes which exist in the cells in an inactive state. According to this view, all enzymes within the genetic capacity of an organism are synthesized. However, many remain inactive because of instability in the absence of substrate. These may be reactivated by vitamin B_{12}.

The key position of glutamic acid in metabolism in the citric acid and urea cycles receives emphasis by many participants. Schema are presented describing the biosynthesis and degradations of histidine, the branched chain amino acids, threonine, the methyl transfer cycle, lysine, the sulfur-containing amino acids, the succinate-glycine cycle, and the aromatic amino acids. A section is devoted to the role of the amino acids in purine synthesis.

New or recent information concerning sites of action of certain vitamins and co-factors is presented. Thus, serine biosynthesis from glycine involves pyridoxal but is enormously accelerated by tetrahydrofolic acid. Evidence that citrovorum factor acts as a co-factor in formate exchange by the way of formyl folic acid is offered. A summary by H. Bentley Glass is helpful.

This new volume in the McCollum-Pratt Symposium series provides stimulating reading in the field of amino acid metabolism. The reviewer considers it to be indispensable to those concerned in anyway with amino acid or protein metabolism. J. G. RHEINHOLD

The Diabetic's Cookbook, by Clarice B. Strachan, with introduction by Charles H. Best, M.D., The Medical Arts Publishing Foundation, Houston, 1955, pp. 304, $6.50.

The author of this cookbook is a homemaker who has developed the recipes during the years of care of her own diabetic son. The recipes have been checked by two dietitians, Mary Ellen Dambold and Julia Ann Barney.

The purpose of this book is "to introduce variety or flexibility into the prescribed diet." Calculations of the recipes are based on the six meal exchange lists. Six recipe sections, namely breads, fat exchanges, fruit exchanges, meat exchanges, milk exchanges, and vegetable exchanges, include those recipes most closely related to each of these exchange lists. Eight major recipe sections—beverages, cakes and cookies, candies, gelatine and pudding desserts, frozen desserts, pastries, salads, and sandwiches—include recipes that may be related to any of the exchange lists. For example, a sandwich may be equally related to the bread and meat exchanges.

Only one recipe is detailed on a page. The calculations for each ingredient are given, and in bold type the exchange value of one serving is indicated. Thus, at a glance the patient may determine whether a recipe will fit into his prescription.

For the most part, family size recipes are given so that the homemaker may use them in her meal planning. The ingredients are those readily available and methods of preparation are clearly given. The recipes using Sucaryl® will be of special interest since they do permit greater variety within a diet prescription.

The cost of the book will, no doubt, be a deterring factor to some patients who might well profit by the guidance provided therein. The author is to be commended for her well organized, clear presentation.

C. ROBINSON

A Pictorial History of Medicine, by Otto L. Bettmann (foreword by Philip S. Hench), Charles C Thomas, Springfield, Ill., 1956, pp. 318, $9.50.

For many years the name "Bettmann Archive" has appeared under some of the most interesting illustrations of historical medicine to be found anywhere. From this vast storehouse (said to contain over one million prints) Otto Bettmann has selected 1000 pictures which highlight medical progress from the Egyptian god, Horos, to Osler, Roentgen and Ehrlich. The pictorial material is supplemented by a lucid running commentary which clearly indicates a wide knowledge of medical history.

As might be expected, the largest section is devoted to medicine in the middle ages. The vividness of many of these prints forms unexcelled teaching material for a proper appreciation of the growth and development of medicine. In addition to medicine as it was practised, there are many pictures of the individuals whose work or personality produced a profound impression on their contemporaries or on posterity.

With an index and a foreword by the Nobel Laureate, Philip S. Hench, this book should prove useful as well as entertaining. The price seems reasonable considering the high cost of publishing pictures at the present time. Any person who has more than a passing interest in the struggles, the victories and defeats, the discoveries and the quackeries of medicine through the ages will enjoy this book. For anyone it will enhance the appreciation of our profession.

S. O. W.

Books received for review by THE AMERICAN JOURNAL OF CLINICAL NUTRITION are acknowledged in this column. As far as practicable those of special interest are selected, as space permits, for a more extensive review.

Of Water, Salt and Life, Lakeside Laboratories, L. W. Frohlich & Co., New York, 1956, pp. 72.

Ageing in Transient Tissues (Ciba Foundation Colloquia on Ageing, Vol. 2), Little, Brown & Co., Boston, 1956, pp. 263, $6.75.

Internal Secretions of the Pancreas (Ciba Foundation Colloquia on Endocrinology, Vol. 9), Little, Brown & Co., Boston, 1956, pp. 292, $7.00.

Cookery Encyclopaedia, Philosophical Library, New York, 1956, pp. 480, $10.00.

Observations on Krebiozen in the Management of Cancer, A. C. Ivy, J. F. Pick and W. F. P. Phillips, Henry Regnery Co., Chicago, 1956, $2.50.

Kenney Visits the Hospital, Julia Ann Bartosh, Exposition Press, New York, 1956, pp. 62, $2.50.

Bulletin World Health Organization, WHO, Geneva, Switzerland, 1956, pp. 837, $2.00.

Experimental Tuberculosis (Ciba Foundation), Little Brown & Co., Boston, 1956, pp. 396, $9.00.

Applied Animal Nutrition, by E. W. Crampton, W. H. Freeman & Co., San Francisco, 1956, pp. 478, $6.50.

History of Hygiene, by H. E. Sigerist, Oxford University Press, 1956, pp. 78, $3.00.

The Use of Chemical Additives in Food Processing, National Academy of Sciences—National Research Council, Washington, 1956, pp. 90, $2.00

Abstracts of Current Literature

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ENERGY REQUIREMENTS IN MAN

One of the most difficult problems involved in arranging therapeutic diets is that of providing the appropriate caloric intake to balance the energy requirements of the individual. These requirements include the calories necessary for basal metabolism, specific dynamic action, physical activity, temperature regulation, and growth and repair of tissues. Probably the most variable of these factors is that of physical activity. A number of nomograms are available which provide approximate caloric requirements necessary in certain occupations. The final proof of caloric adequacy of the diet is found in the body weight curve and performance of the individual.

Energy Expenditure in Relation to Nutrition. O. G. Edholm. *Proc. Brit. Nutrition Soc.* 15: 80, 1956.

The two sides of the energy balance have had uneven treatment in the past. Calorie intake has been very thoroughly investigated. Tables giving the calorie values of nearly all foods and drinks are available. There is also a considerable literature on the energy expenditure on particular activities, but less information on total energy expenditure. The limitations of a direct calorimetry are the expense of the construction of a suitable chamber, the restriction imposed on the activity of the subject, and the fact that such investigations must be made in the laboratory. Indirect calorimetry can be used, and in practice energy expenditure is measured by recording for brief intervals and applying the values obtained for the whole period occupied by that activity. For calculating energy expenditure the following information is necessary: (1) a list of the activities of the day and the time spent on each; (2) the energy expenditure on each of the activities.

The simplest type of calculation would be one which has been frequently used, i.e., division of the day into 8 hours' sleep, 8 hours' work, and 8 hours' recreation. The caloric expenditure during sleep can be taken as equal to the basal metabolic rate. The 8 hours off work can be assumed to be about 3 x B.M.R., leaving the energy expenditure during work as the main variable, and studies outside the laboratory have been mainly concerned with this variable. Many published values can be found for the calorie cost of different occupations, and it has been possible to compute the total energy expenditure of, for instance, coal miners, bricklayers, clerks, etc.

The results obtained from the measurement of energy expenditure cannot replace the information obtained in nutritional surveys. A knowledge of the total energy expenditure is of no assistance in assessing the nutritional quantities of the diet as regards vitamin or mineral requirements or the balance between protein, fat, and carbohydrate. It would be an error to conceive of the measurement of energy expenditure as replacing a dietary survey, except for a figure of total calorie intake needed to balance the output.—B. SURE

Information concerning the energy expenditure involved in various occupations is of importance to those interested in nutrition and industrial medicine and to social and health agencies. Broad studies of the type reported below are necessary to supply the required data.

Studies on Expenditure of Energy and Consumption of Food by Miners and Clerks, Fife, Scotland, 1952. R. C. Garry, R. Passmore, G. M. Warnock, and J. V. G. A. Durnin. *Med. Res. Council Spec. Rep. Ser.* No. 289, 1955, H. M. Stationery Office, London, pp. 70, 5*s*.

In 1952 a survey of energy expenditure in relation to

dietary intake was made by a committee of experts appointed by the Medical Research Council. Nineteen underground miners and ten colliery clerks were very carefully studied for one week. Two features of the experiment were (1) the use of the Kofranyi-Michaelis respirometer—a light dry gas meter which could be worn during heavy work, and (2) a study of the energy expenditure for 24 hours a day rather than merely when the men were occupied at a specific job.

The details are clearly presented and will be of great interest to most readers. In general, it was found that the daily energy expenditure of the miners, all of whom performed hard labor during their working hours, averaged 3660 cal; this was 860 cal greater than the expenditure of the sedentary clerks. However, identical energy was expended by clerks and miners during rest or while off duty and at home. Thus the difference in caloric expenditure was due to the physical work done. As would be expected, miners took in 990 more calories than the clerks each day. The percentage of calories derived from protein, fat, and carbohydrate was essentially the same for both groups, and miners did not draw on predominantly high carbohydrate foods for their extra calories.—S. O. WAIFE

The need for increased energy expenditure for successful programs of weight reduction is re-emphasized in the following.

Daily Energy Expenditure in Man. R. Passmore. *Proc. Brit. Nutrition Soc.* 15: 83, 1956.

In western Europe, in North America, in Australia, and in New Zealand, the daily energy expenditure of large numbers of the population is less than the energy derived from their food. In consequence the people become fat. In Asia, in Africa, and in many countries in Latin America, the food supply is insufficient to meet the energy needs of daily life. As a result, many persons in these countries are thin, and also become lethargic. There is a consensus of medical opinion that such caloric imbalances are detrimental to health and working efficiency. Our civilizations are failing either to disperse people throughout the world to the agricultural sources of available food, or, alternately, to distribute foods by the mechanism of international trade, according to the physiologic needs of the population. The latest data from FAO (1955) indicate that the disproportions in the distribution of food are increasing rather than diminishing.

A reducing diet is not a safe procedure for obtaining permanent weight reduction, unless it is accompanied by sufficient energy expenditure, which can only be accomplished by adequate daily activities. In a recent study in Boston, three large groups of obese persons were (a) left untreated, (b) referred to a hospital dietary clinic, and (c) subjected to group dietary therapy. After two years no difference was apparent between the groups and, generally speaking, there was no improvement. Immediate loss of weight at the beginning of various treatments was not permanent.

According to Mayer (1955) of the Department of Nutrition, Harvard School of Public Health, our appetite was never designed as a food-regulating mechanism for persons who spend most of their lives seated on a chair. The first object in the treatment of obesity is to get the patient active and increase the daily energy expenditure. By walking hard for half an hour in the morning and again for half an hour in the evening an obese person may burn off one ounce of fat. If this procedure is continued for a year, then over 20 pounds of fat will have been oxidized. More important, this regular increase in daily energy expenditure may set the appetite-regulating mechanism aright and thereby provide the necessary conditions for rendering practical the advice given by dietitians.—B. SURE

The energy requirements for girls, men, and athletes are reviewed. It is of interest that the average fecal caloric loss was only 3 per cent of the intake in the study conducted on pre-adolescent girls. This low value reflects the high absorption of the special diets employed.

Metabolic Studies with Pre-adolescent Girls. II. Energy Absorption. R. M. Patrick, P. S. Richardson, and D. S. Moschette. *J. Am. Dietet. A.* 31: 138, 1955.

The energy absorption (caloric intake, minus the fecal calories lost) was determined for six girls 8 to 11 years of age. This study, conducted for 56 days, was an auxiliary to one reported earlier on carotene utilization. Caloric intake and fecal loss determined by analyses for each girl during eight periods of five or seven days' duration showed a mean daily intake of 2097 calories for all subjects for the entire experiment. The average fecal loss was 60 calories. In several comparisons the authors reported a direct relationship between the caloric intake and caloric loss per kilogram of body weight. The mean daily caloric intake per kilogram for the group was 77.7 calories and the average loss was 2.3 calories. Thus, by difference, the mean daily absorption was 75.4 calories per kilogram. No direct relationship was found between mean total caloric intake per kilogram and the caloric absorption per kilogram (correlation coefficient 0.998). The mean caloric loss for the group was 2.9 per cent and mean caloric absorption 97.1 per cent of the intake.

The authors comment that this value is higher than the range of 94.3–96.0 per cent previously reported from five laboratories. They further suggest that the specially controlled diet of the pre-adolescent girls may have accounted for the higher figure, since the diet contained a large amount of highly digestible animal protein and little roughage or indigestible material.

Inclusion of a sample menu and weights and weight changes of the subjects would, in the opinion of the reviewer, have added to the interest of the paper.—J. M. SMITH

The Energy Expenditure and Food Intake of Individual Men. O. G. Edholm and J. G. Fletcher. *Brit. J. Nutrition* 9: 286, 1955.

Within the past two decades there has developed an interest in the importance of calorie expenditure and its relationship to intake. There have been two main reasons for this: the first has been a desire to find out more about the mechanisms which relate intake to expenditure—i.e., what regulates appetite—and the second an interest in industrial and field physiology.

The individual expenditures of energy in a homogeneous group of 12 young men, cadets in a military training establishment, were investigated daily for a fortnight by direct measurement coupled with an exact diary and timing technique. The expenditure varied widely from day to day. The individual food intakes were also measured daily and varied equally widely. The weekly and fortnightly balances between the two agreed when they were averaged, but there was no correlation between the mean expenditure on any one day and the intake two days later. The energy expended on any one task, particularly a basal one such as sitting, lying, or standing, often varied very much from one man to the next. The energy expended by a number of men on tasks has been given in detail for future reference.—B. SURE

Energy Expenditure in Athletic Activities. H. R. Noltie. *Proc. Brit. Nutrition Soc.* 15: 93, 1956.

The energy expenditure in athletic activities seems to range from the extraordinarily high figure of 150 cal/minute for "sprint-like" activities, lasting 20 seconds or less, to one-fifth of that output for "endurance" activities, lasting up to half an hour. But measurements have only occasionally been made outside laboratory conditions, and few are available for present-day athletes of the "world class," so the figures recorded in the literature are to be regarded as only first approximations.—B. SURE

NUTRITION PROJECTS AND SURVEYS

The initial abstracts below present a review of the functions of the three principal organizations involved in nutrition on a world-wide basis today. To those who are familiar with the work of these groups through their publications and reports, it may come as a surprise to note that these efforts are being conducted by relatively small staffs. There can be no doubt that great impetus has been given by these groups to research into food and agricultural technology in distressed areas of the world, in addition to the direct provision of foodstuffs distributed by them to deprived peoples. Through their continued efforts much suffering and disease will be alleviated.

Food and Agriculture Organization (FAO) and Nutrition. W. R. Aykroyd. *Proc. Brit. Nutrition Soc.* 15: 4, 1956.

The Nutrition Division: FAO has five divisions: Nutrition, Agriculture, Fisheries, Forestry, and Economics. The Nutrition Division is the smallest of the divisions, employing some 19 professional staff members, some 13 of whom are stationed in headquarters in Rome, Italy and the remainder in regional offices in Washington, Santiago, Cairo, and Bangkok. The staff of 19 includes 14 different nationalities. Two sections forming part of the Division may be mentioned, namely, the Food Consumption and Management Section and the Home Economics Section. The Division has responsibility for home economics and certain aspects of food technology, as well as for nutrition itself. Apart from the regular staff, specialists are employed in field assignments under the Expanded Technical Assistance Program (ETAP). In the middle of 1955 there were 25 ETAP specialists working in some 17 countries, of whom 9, 10, and 6 will be concerned with nutrition, home economics, and food technology, respectively. Between 60 and 70 per cent of the expenditure under ETAP falls under the head of Agriculture by FAO.

The main objective of the Nutrition Division of FAO is to help people get enough of the right sort of food to eat. Other objectives are training nutrition workers, teaching peoples in their homes, and assisting in child nutrition and school feeding programs.—B. SURE

World Health Organization (WHO) and Nutrition. R. C. Burgess. *Proc. Brit. Nutrition Soc.* 15: 13, 1956.

The Nutrition Section of WHO is a small unit. Until recently it consisted of a Section Chief only, but has now been strengthened by the appointment of a second health officer with experience in nutritional problems. It has, however, the cooperation of the other sections in the Division—particularly those dealing with maternal and child health and health education of the public. WHO is concerned with all aspects of health, and malnutrition is probably one of the most important causes of ill-health throughout the world today. In many countries a combination of disease and malnutrition exists and is responsible for high mortality and morbidity rates in the younger age groups, an example of which is kwashiorkor, which is the most widespread nutritional problem affecting the general standard of public health in the world today. More effective control of the intercurrent infections and infestations has now made it possible to see the full significance of malnutrition as a public health problem. WHO assists in combating endemic goiter with potassium iodide, kwashiorkor with good quality high protein foods (dried milks, soybean and fish flours) and with vegetable protein substitutes for cow's milk. It helps in the conquest of pellagra with adequate diets and assists in education of the best use of locally available foods.—B. SURE

The United Nations Children's Fund (UNICEF) Assistance for Child Nutrition. Secretariat of UNICEF. *Proc. Brit. Nutrition Soc.* 15: 22, 1956.

By the end of 1955, after nine years' operation,

UNICEF will have shipped, or allocated for shipment, a total of about 700,000,000 pounds of dried skim milk. In addition, it will have allocated the equivalent of over $12,000,000 for milk conservation projects. The function of three agencies, FAO, WHO, and UNICEF, is to aid government programs that result in benefit to children. For UNICEF, however, it is the exclusive function.

UNICEF has not only given an impetus to child feeding programs but has popularized the importance of milk in children's diets and has focused attention generally on child nutrition. The next step was to aid the countries in establishing permanent facilities for collecting, conserving, and distributing safe milk from local sources to replace the imported supplies, and to do it in such a way that the countries would be able to provide free or low-cost milk to large numbers of children. UNICEF provided the important equipment required for drying and pasteurizing plants; the governments provided buildings, auxiliary equipment, machinery and labor, averaging in value about five times more than the UNICEF contribution.

The bulk of UNICEF aid has been for the control of communicable diseases affecting children (malaria, tuberculosis, yaws, syphilis) and for maternal and child welfare services, mainly to rural centers. As with school feeding programs in Europe, there was sufficient experience and technical knowledge to indicate a clear path of action by which UNICEF supplies and WHO technical advice could be combined to aid government programs in these fields along lines that were economically practical and gave reasonable assurance of effective long-range results.

Tests of acceptability of fish flour sponsored by FAO with fish flour supplied by UNICEF are under way in a number of countries. In Indonesia, UNICEF is aiding in the erection of a plant to produce dried vegetable milk based upon the soybean as a food for infants, to be distributed through maternal and child welfare clinics and hospitals.—B. SURE

The remaining abstracts deal with representative nutritional surveys in various countries, including Egypt, Burma, Uganda, Britain, and the United States. The specific nutritional needs of the areas involved in the first three studies have been clarified by careful analysis of available foodstuffs and methods of food preparation. Recommendations for the planning of practical programs in nutrition and home economics can be based upon the findings. In the surveys reported by United States workers, biochemical data and dietary intake provide the respective bases for nutritional evaluations in the two reports. The British report deals with long-term surveys which, although conducted with only two subjects, provide the information that there may be little advantage gained by using the longer period.

Nutrition and Home Economics Program in Egyptian Villages. M. A. Ross. *Proc. Brit. Nutrition Soc.* 15: 30, 1956.

In 1953 the Government of Egypt and FAO jointly undertook a demonstration project in agriculture, rural industries, nutrition, and home economics, the object of which is to improve the standard of living of the Egyptian village population. The sponsoring ministry for the Government was the Ministry of Agriculture. Five villages in the Nile Delta about 45 kilometers northwest of Cairo were selected for the demonstration.

A considerable number of nutritional investigations have been made in Egypt. Some of these have been concerned with broad problems of nutrition and measures to solve them, some with pellagra, and others with parasitism and malnutrition and how they interact to impair the health of the population. Miss Ross's work has not followed these lines. She began by investigating foods used, methods of preparation, eating habits, child feeding practices, household equipment, and family life, in order to find simple, inexpensive, and acceptable steps that might be taken to improve the diets and living habits of the people. With the help of two young Egyptian women, a comprehensive study of 23 families in one village was undertaken as a basis for planning practical programs in nutrition and home economics education.

Families who possess a *gamoosa* (the big dark grey buffalo of Egypt) usually make butter daily, churning the whole milk in goatskin bags and selling butter for cash. They make a fresh white cheese from the buttermilk, using a piece of calf's stomach as a starter. The *gamoosa* is probably the greatest single asset in the economy of village families. It provides the chief source of animal protein in the diet, fuel for cooking, and power to run the irrigation pump and to plough the land, as well as being a source of income when butter or whole milk is sold. It shares the family home along with the donkey, goat, sheep, chickens, and rabbits.

Eggs are usually sold or bartered to obtain sugar, tea, soap, or vegetables. They are occasionally eaten by the men or older boys, but since they are considered to cause "liver disease," they are generally avoided. Meat is eaten once or twice a week by the more prosperous; but by poorer families, which constitute by far the larger portion of the Egyptian population, meat is eaten only once or twice a month or only on the six feast days of the year. The Egyptians use excessive amounts of tea and sugar, and their diet is markedly deficient in good quality proteins.—B. SURE

Nutrition Work in Burma Past and Present. S. Postmus. *Proc. Brit. Nutrition Soc.* 15: 35, 1956.

Though the number of nutrition workers in Burma has been very limited, various kinds of nutrition work have been carried out. The nutritional survey conducted in Burma in 1939, 1951, and 1948 was published in 1948 by the Government Printing Office in Rangoon and may be summarized as follows: The calorie and total protein intake was not always sufficient. The calcium content of the diet was generally low. The

iron content was several times below the standard of 20 mg daily. Many diets did not contain sufficient vitamin A and carotene. When no home-pounded rice was consumed, the thiamine content was inadequate. Often the ascorbic acid content of the diet did not reach the standard of 30 to 50 mg/consumption unit/day. The deficiency signs found in the nutritional surveys, xerophthalmia, phrynoderma, hyperkeratosis of the skin, angular stomatitis, caries of the teeth, pyorrhea and retracted gums, corresponded to the deficiencies in the diet.

Various posters have been drafted, one on the correct method of washing rice, one on the choice and the preparation of vegetables, and one on the basic three foods for Burma. During some field surveys short talks adapted to the specific needs of the area were given to the local workers and villagers. UNICEF is providing milk powder and fish-liver oil capsules to the government under the Maternal and Child Health Program for feeding women and children in Maternal and Child Health Centers, schools, children's institutions, and hospitals.

That the international organizations realize the importance of improving the nutritional status of Burma becomes clear through the fact that not only WHO and FAO are assisting Burma in this field, but that the Ford Foundation has granted a large sum of money for equipment and fellowships for in-service training, and that the Colombo plan allows for provision of the money for fellowships in the nutrition field.—B. SURE

An Investigation of the Daily Intakes of Food of Individual Boys at a Boarding School in Uganda. R. Schwartz and R. F. A. Dean. *Brit. J. Nutrition* 9: 230, 1955.

Individual food intakes of boys from 9 to 20 years old, chiefly Baganda, were measured at a boarding school in Uganda, for three periods: (1) when the school diet was unpopular and limited in amount (30 boys); (2) when the school diet was popular but still limited (32 boys); and (3) when the popular school diet was offered in an unlimited amount (19 boys).

All the food intakes were below 90 per cent of those of British boys of the same ages, even when unlimited school food was offered. The intakes bore no relation to age, but well-grown children at any age had better appetites than those who were less well grown. The intake did not increase when unlimited school food was offered, possibly because the bulkiness of the diet made larger amounts unacceptable.

All the boys supplemented the school food with extras which accounted for one-third, one-fourth, and one-fifth of the total intakes in periods 1 to 3, respectively. The most important extra item was sugar, which was taken chiefly in tea in large quantities. Although some of the boys were underweight by British standards, no definite signs of undernutrition were seen.

The implications of the findings are discussed in relation to the customary diet of the boys, and it is stressed that the supplementation of African diets, however justifiable it may be in theory, needs first the foundation of exact experiment.—B. SURE

Nutritional Status of School Children 15 and 16 Years of Age in Three Idaho Communities. Blood Biochemical Tests. S. V. Bing, K. P. Warnick, and E. Woods. *J. Nutrition* 57: 29, 1955.

This study was part of a cooperative project on the nutritional status of population groups in selected areas of the West. In the Idaho phase of this project biochemical determinations were made on fasting venous blood samples from 280 school children 15 and 16 years of age in three communities.

The mean value for the girls was significantly higher than for the boys for sedimentation rate and for ascorbic acid, free cholesterol, and copper of serum. The mean value for the boys was significantly higher than for the girls for serum alkaline phosphatase, hemoglobin, and packed cell volume. The 15-year-old subjects had a mean serum alkaline phosphatase value significantly higher than the older children. The subjects in the northern community had mean serum carotene and copper values significantly lower than the subjects in the two southwestern communities. The blood values of the girls and boys are compared to suggested limits of normal.

Highly significant positive correlations were found for both girls and boys between the following comparisons of whole blood and serum constituents: vitamin A and carotene; vitamin A and both free and total cholesterol; carotene and both free and total cholesterol; carotene and ascorbic acid; free and total riboflavin; free and total cholesterol; copper and sedimentation rate; hemoglobin and packed cell volume. In many of the other comparisons, only the data of the boys showed highly significant correlations. Further work is recommended to explain these sex differences.—B. SURE

Nutritional Intake of Children. III. Thiamine, Riboflavin, and Niacin. V. A. Beal. *J. Nutrition* 57: 183, 1955.

This series of papers is intended to present the picture of nutritional intake during the first five years of life by a group of healthy children living at home. Data have been presented from 934 nutrition histories on 63 children in the first five years of life. Thiamine, riboflavin, and niacin intakes have been computed in terms of quartiles and maximum and minimum levels observed. Some individual patterns of intake are shown.

The intake of thiamine rises steadily during the first 15 months, then reaches a plateau which is maintained until just after three years, after which it increases again. The median of these data is slightly above the National Research Council Recommended Allowance.

The riboflavin intake, after an initial rise in the first year, decreases in the second and third years with a decrease in milk consumption, then rises again between

three and five years. More than 75 per cent of the children in this group consume an amount of riboflavin greater than the Recommended Allowance throughout this age period.

The niacin intake tends to increase throughout this age span, although the children with high intakes during the second year are likely to show a decrease during the third year. Although only 25 per cent of the children meet the Recommended Allowance, there is no evidence that their intake is inadequate, as judged by growth rate and absence of deficiency symptoms.—B. SURE

Long-Term Individual Dietary Surveys. G. M. Chappell. *Brit. J. Nutrition* 9: 323, 1955.

The literature on dietary surveys indicates that short duration cannot be relied on to give a true picture of the normal dietary pattern. It was, therefore, decided to record for long periods the intakes of foods and nutrients in the normal diet of two healthy adults pursuing their customary occupations. By "healthy" is meant the existence of a feeling of well-being, a steady body weight, good physique, and sufficient energy to perform the normal activities of the subjects studied.

One subject was a man aged 66 years whose study lasted for 13 consecutive weeks; the other subject was a woman aged 34 years whose study lasted for 61 weeks and later for another 9 weeks. The diets were weighed by each subject and the calories and nutrients in them calculated from food tables. Comparison of these two studies shows that caloric intake was identical in both and that average intakes of most nutrients were larger in the shorter study, generally by very small amounts. Having regard to alterations in dietary habits over a span of 18 months, these changes are readily explained, and it is remarkable that caloric and nutrient intake did not vary more.

Since only two individuals were involved, this study could hardly be considered as a "survey," which should comprise at least dozens, if not hundreds, of individuals. —B. SURE

PYRIDOXINE

The early lesions observed in the arteries of patients with atherosclerotic disease consist of a deposition of mucoprotein material in the intima, with fibroblastic proliferation and alterations in the elastica; these lesions have been observed in several animal species maintained on a pyridoxine-deficient diet. As the lesion progresses, there are increasing amounts of lipids and calcium, giving rise to the sclerotic plaques. Such observations have given rise to speculations concerning the possible role of vitamin B_6 deficiency as a factor in human atherosclerosis. Many aspects of this problem are discussed in a symposium issue (July-August, 1956) of this JOURNAL.

Is Atherosclerosis a Conditioned Pyridoxal Deficiency? H. A. Schroeder. *J. Chronic Dis.* 2: 28, 1955.

According to Schroeder, there is some evidence that human atherosclerosis is influenced by vitamin B_6 deficiency. First, it is claimed that "it is entirely possible that the American adult is maintained on a marginal intake of this important coenzyme," especially during periods of the year in which fresh fruits and vegetables are not available, and if processed foods are extensively used. If it can be shown that pyridoxine deficiency can condition atherosclerosis, this dietary distribution would help explain the extent of atherosclerosis (and hypertension) in the most "civilized" countries.

Pyridoxine appears to be essential for the formation and utilization of unsaturated fatty acids. The author's theory is concerned with an abnormal saturated-unsaturated fatty acid ratio in cholesterol esters "induced by an excessive ingestion of warm-blooded terrestrial animal fat." In addition to nutritional pyridoxine deficiency, the American human body is said to contain many abnormal trace elements (e.g., cadmium) which could compete for an essential metal in the vitamin-enzyme system and produce a conditioned deficiency.

Thus civilization may be said to impose three stresses: a marginal intake of vitamin B_6, exposure to exogenous trace metals in abnormal amounts, and an excessive dietary intake of saturated fatty acids. The arterial pressure and cholesterol ingestion may be of "secondary" importance. The author points out the obvious need for further research work. Little or no experimental evidence is said to exist against this interesting hypothesis.

Although on first reading this article one is overwhelmed by skepticism, if not disbelief, rereading suggests the plausibility of the speculation. The hypothesis is ingenious. However, it seems to this reviewer that the author has perhaps oversimplified a highly complex problem: the paper deserves wide readership, nevertheless.—S. O. WAIFE

Although pyridoxine requirements in human nutrition have not been established, the vitamin has been shown to be an essential dietary factor. A well-defined syndrome has been observed in infants receiving pyridoxine-deficient formula diets. Information concerning the pyridoxine content of milk and other infant feeds is necessary.

The Pyridoxine Content of Breast-Milk. W. Neuweiler and H. Fischer. *Intern. Ztschr. f. Vitaminforsch.* 25: 205, 1954.

The pyridoxine content of human and cow's milk was determined microbiologically, by methods detailed in the paper. The normal pyridoxine content of human milk was found to be about 15–20 μg per 100 ml (with wide variations), as compared to 120 μg per 100 ml for cow's milk. Most of the determinations were done on early milk, but the authors' results indicated that later milk (14 days or more after delivery) has a higher pyridoxine content.

Pyridoxine administration to lactating women was followed within a few hours by a three-fold rise in

pyridoxine content, but the level fell again after 9 hours to a level which was only slightly elevated. If pyridoxine administration was continued, accumulation occurred, but only up to the third day, after which the pyridoxine content decreased despite continued loading with the vitamin.—C.-J. HOWELL

There are considerable species differences observed in the effects of pyridoxine deficiency and in the influence of stress upon pyridoxine metabolism. The application of experimental observations concerning this vitamin to clinical situations has not been rewarding.

Nitrogen Metabolism in Vitamin B_6 Deficiency in the Dog. W. W. Hawkins and E. G. Young. *Am. J. Physiol.* 181: 196, 1955.

Although blood urea, production of urea, and nitrogen excretion are increased during vitamin B_6 deficiency in the rat, this is not the case in the dog. Increased production of urea was evaluated by using test loads of amino acids. Desoxypyridoxine, a pyridoxine antagonist, produced a minor increase in nitrogen excretion during vitamin B_6 deficiency. Plasma proteins were found to be unchanged in pyridoxine deficiency.—M. J. OPPENHEIMER

Effects of Anorexia and X-Irradiation on Vitamin B_6 Excretion in Rats. C. S. Song, W. N. Pearson, and W. J. Darby. *Am. J. Physiol.* 184: 309, 1956.

Adult female albino Sprague-Dawley rats subjected to 500 r (backscatter) of whole-body x-irradiation exhibit an increase in the urinary excretion of the B_6 group of vitamins, beginning on the second day after irradiation. However, control animals, whose food intake was limited to that of the irradiated group, excreted amounts of vitamin B_6 that were quantitatively similar. It is concluded that the increase of vitamin B_6 excretion found after x-irradiation is a reflection of the irradiation-induced anorexia and is not due to tissue changes brought about by irradiation per se.—AUTHORS

THE SPRUE SYNDROME

The sprue syndrome has engaged the attention of clinicians and investigators in increasing numbers throughout the world. One reason for this may be the fact that its victims provide an excellent example of general nutritional depletion involving all essential food factors, including electrolytes and water, permitting intricate biochemical and physiologic studies not readily encountered elsewhere. In addition, there is the challenge of determining the elusive pathogenesis of the diverse conditions giving rise to the syndrome, and finding improved methods of treatment. The reward for these efforts has come recently with respect to celiac disease, which, in many instances, has been due to gluten sensitivity. The following review article is highly recommended.

The Sprue Syndrome. J. C. S. Paterson. *Am. J. Med. Sc.* 231: 92, 1956.

The diagnosis of sprue syndrome is being made with increasing frequency in many parts of the world, possibly owing to improved recognition of its clinical manifestations and an awareness of the latent or mild forms of the disease. The sprue syndrome comprises celiac disease, nontropical and tropical sprue. A heredofamilial incidence is recognized. The recognition is aided by roentgenographic study of the small intestine, by hematologic examination, and by demonstrating excessive excretion of fat in the feces. Opinions vary on the usefulness of vitamin A absorption curves and postalimentary chylomicron studies. Pancreatic disease may be differentiated by assay of the enzymes in the duodenal contents.

Advances in treatment have come rapidly in recent years. The removal of wheat and rye gluten from the diet of patients with celiac disease has proved beneficial in a large number of children with this disease. Dramatic remissions of sprue are reported following corticotropin (ACTH) and steroid hormone therapy; relapse occurs frequently upon withdrawal. Hematologic remissions in tropical sprue follow the use of folic acid, vitamin B_{12}, liver extract, and yeast preparations. Antibiotic agents have also been successful. Changes occurring in the intestinal flora of organisms may result in competition for available B vitamins and worsen the condition in a vicious cycle.—C. R. SHUMAN

Data concerning the condition in later years of patients treated in childhood for celiac disease are beginning to accumulate. The studies reported have demonstrated that the disease persists, often in milder form, into adulthood.

The Duration of Celiac Disease. C. P. Katsampes, A. B. McCoord, E. Hawley, and J. Connelly. *Am. J. Dis. Child.* 90: 634, 1955 (Soc. Trans.).

Twenty cases of celiac disease of chronologic ages 7 to 35 years, in whom the diagnosis had been established 6 to 25 years previously, were studied for persistence of their celiac symptoms and absorption of vitamin A ester. Twelve cases still had symptoms of their disease, and 17 cases had either poor or definitely diminished absorption of vitamin A ester from the gastrointestinal tract.

From the results, it is concluded that idiopathic celiac disease persists for years, into adulthood. Although the symptoms tended to lessen, they did not disappear completely in a majority of the cases observed. The continued poor or diminished vitamin A ester absorption showed continued defective absorption or metabolism by the intestinal mucosal cells. The absorption test alone may be useful as a guide to the status of a celiac patient. The results also indicated that the usual and known methods of treatment seldom achieve "cure," if such occurs in this disease. The results confirmed those of di Sant' Agnese (1953) and

extend the known duration of the disease.—J. N. ETTELDORF

The finding of a specific biochemical abnormaltiy in the metabolism of patients with celiac syndrome would represent a signal advance, providing a diagnostic tool for a disease which is often diagnosed by exclusion. Confirmation of this finding is eagerly awaited for its potential usefulness in diagnosis.

Excretion of Ethanolamine-Phosphoric Acid in Coeliac Disease. (A Preliminary Communication). O. D. Fisher and D. W. Neill. *Lancet* 1: 335, 1955.

The urines of 53 children suffering from celiac disease were examined by paper chromatography. In 30, a spot was found corresponding to ethanolamine-phosphoric acid. It occurred at all ages and was independent of diet or of the stage of the disease.

The authors have done 709 urinary amino acid chromatograms in 606 patients, 225 of whom were adults. In addition to the 30 cases of celiac disease, 16 showed the substance corresponding to ethanolamine-phosphoric acid. Five were infants less than a month old (4 had erythroblastosis and the other "loose motions"); 4 other children were suspected of celiac disease; there were 3 siblings of celiac patients; one child had "lienteric" diarrhea; one infant vomited and failed to thrive; and a girl of 8 had repeated fractures and steatorrhea. The only adult was a man of 42 who died following obstructive jaundice.—F. E. HYTTEN

In sprue, anemia of a macrocytic or hypochromic type may be observed due to an insufficiency of vitamin B_{12}, folic acid, or iron. Correction of the anemia requires replacement of the deficient eythropoietic factors and usually depends on improvement in the intestinal symptoms, indicating a remission in absorption defects. In some instances, active sprue without anemia has been observed, casting further doubt upon the already tenuous theory that folic acid or vitamin B_{12} deficiency may be responsible for the syndrome.

A Preliminary Study of Small Bowel Mucoproteins in Tropical Sprue. F. H. Gardner and C. Romero. *Am. J. Med. Sc.* 231: 82, 1956.

The presence of symptoms of sprue despite a hematologic remission has cast doubt on the explanation of a nutritional deficiency of folic acid or vitamin B_{12} as the sole cause of this syndrome. It has been suggested that mucous secretions of the small bowel may be abnormal in sprue and interfere with fat absorption. In this study, gastric and jejunal juices were obtained through double-lumen intestinal tubes for analysis of the dissolved mucoproteose and mucoprotein fractions, using the method of Glass and Boyd. The results are reported as showing no differences in the mucin, mucoproteose, or mucoprotein contents in gastric juices of controls and patients with sprue. In the succus entericus, there was a lower contentration of mucoprotein in the sprue patients than in the controls. The authors suggest that alterations in the content or amount of dissolved mucoprotein may reflect changes in the mucosal surface of the small intestine that impair absorption of foodstuffs.—C. R. SHUMAN

CARBOHYDRATE METABOLISM

The utilization of glucose derived from dietary carbohydrates represents one important source of fuel and energy for all tissues. However, there are many other uses to which glucose may be put by the cells, such as glucuronide formation in liver, hexosamine production, lipogenesis, pentose conversion, etc. The ability of the liver and other tissues to utilize glucose efficiently appears to depend upon diurnal operation of the glycolytic enzymatic reactions. With high fat diets or starvation, the hepatic utilization of carbohydrate is temporarily suppressed.

Influence of Previous Diet on Hepatic Utilization of Glucose in Vitro. J. E. Whitney, S. Roberts, and E. L. Beaver. *Am. J. Physiol.* 182: 51, 1955.

In these experiments on Sprague-Dawley rats the effects of high carbohydrate and high fat diets were observed. These diets were followed by a bout of fasting. The parameter studied was the *in vitro* hepatic utilization of glucose. Carbon dioxide production and glycogenesis from glucose were depressed in liver slice by a regimen of a high fat diet lasting for two or three months. Effects of fat and carbohydrate diets on hepatic glucose oxidation persisted for one to two days after institution of the fasting period. The caloric content of the diet and the duration of a short-term fast did not play a role in total oxidative metabolism in the liver. Hepatic carbohydrate metabolism depends on the dietary levels of carbohydrate. Liver slices from animals on a high fat diet preferentially oxidize a substrate which is not glucose.—M. J. OPPENHEIMER

The underutilization of glucose due to insulin deprivation in diabetes appears to be firmly established as the basis for this disease. The degree of insulin deficiency varies widely and is conditioned by many factors. With correction of certain of these factors, such as obesity, excessive caloric intake, and illness, a mild insulin deficiency may be ameliorated. The C^{14}-labeled glucose studies are helping to clarify these concepts.

C^{14} Studies in Carbohydrate Metabolism. II. The Oxidation of Glucose in Diabetic Subjects. W. W. Sheeve, N. Baker, R. A. Shipley, G. E. Incefy, and J. W. Craig. *Metabolism* 5: 22, 1956.

Single injections of trace amounts of uniformly labeled C^{14}-glucose provided data on total glucose, volume of glucose distribution, fractional rate of replacement, and oxidation rate of glucose in eight diabetics and four normal subjects. The insulin-de-

prived, hyperglycemic, nonketotic diabetics had expired CO_2 values equivalent to those of the normal subjects. The remaining diabetics manifesting ketosis gave values lower than the normals; the rate of oxidation of glucose was depressed below normal in three diabetic patients with ketosis. The glucose pool was calculated as 24 per cent of body weight in normals, 26 per cent in stable diabetics, and 30 per cent in labile diabetics. The mean rates of glucose turnover were 0.085 g, 0.10 g and 0.19 g per kg per hour in the three respective groups. The decreased rate of oxidation of glucose to CO_2 in the labile diabetics may indicate that a greater degree of insulin deprivation existed in these patients. The normal oxidative rate in diabetics without ketosis suggests that residual insulin activity remains despite withdrawal of the exogenous supply. Perhaps in the latter group the destruction or inactivation of insulin is not as rapid as in the former.—C. R. SHUMAN

The profound effects of certain adrenal steroids upon carbohydrate metabolism have been reviewed below by workers who have contributed extensively to this field.

Influence of Adrenal Cortical Steroids on Carbohydrate Metabolism in Man. J. W. Conn and S. S. Fajans. *Metabolism* 5: 114, 1956.

The principal glucocorticoid secreted by the human adrenal cortex is hydrocortisone, which affects the metabolism of carbohydrate by inhibiting peripheral glucose utilization and by increasing gluconeogenesis from protein. In larger doses, compounds A and B have a similar effect, while desoxycorticosterone and aldosterone are inactive with respect to glucose metabolism. In Addison's disease, extreme sensitivity to insulin is observed; when coexistent with diabetes, treatment of adrenal insufficiency with steroid hormones intensifies the diabetic state. There is, however, less susceptibility to hypoglycemic episodes. In Cushing's syndrome due to excessive secretion of hydrocortisone, a loss of carbohydrate tolerance is commonly observed. When diabetes results, the patient may be relatively insensitive to insulin and ketosis is rare. "Steroid diabetes" in Cushing's syndrome is reversible after removal of the adrenal lesion. The administration of corticotropin (ACTH) or adrenal steroid hormones may produce a similar decrease in carbohydrate tolerance. In addition, a reduction of the maximum renal tubular resorptive capacity for glucose has been demonstrated during steroid hormone therapy. Stressful experiences have been observed to produce a loss of carbohydrate tolerance attributed to adrenal cortex secretions. The primary effect of adrenal steroids administered to the potential diabetic has been used to bring to light a subclinical defect in carbohydrate metabolism. Adrenal cortical function in diabetics may be decreased, as demonstrated in several studies. On the other hand, increased adrenal function has been proposed as an important factor in the pathogenesis of the Kimmelsteil-Wilson lesion. In diabetic acidosis, enhanced adrenal function is apparently a late manifestation. Adrenal steroids and ACTH have been employed with considerable success in the management of spontaneous hypoglycemia and in the preoperative preparation of patients with hypoglycemia.—C. R. SHUMAN

In evaluating carbohydrate metabolism clinically, the glucose tolerance curve following an oral glucose load is widely used. While this procedure is more generally recommended than is the intravenous method, it must be recognized that there are many conditions which will influence the curve in either direction. The "flat" curve is one which we commonly encounter; the interpretation of this finding is discussed.

A Study of the "Flat" Oral Glucose Tolerance Curve and Its Relation to Rate of Emptying of the Stomach. C. E. Test, R. L. Nichols, R. L. Landau, H. T. Ricketts, and R. Longhead. *Am. J. Med. Sc.* 231: 69, 1956.

The flat blood glucose curve is defined as one in which the maximum rise of venous blood glucose in a 3-hour period after a standard oral dose of glucose is less than 30 mg per 100 ml; these curves have been associated with hypopituitarism, Addison's disease, myxedema, anorexia nervosa, and steatorrhea. This study is concerned with similar flat curves observed in 26 patients in the absence of the above conditions. The rate of gastric emptying was observed fluoroscopically by simultaneous administration of barium with the glucose. By this procedure it was not possible to relate the flat glucose tolerance curve to a delay in gastric emptying. In 15 of the 26 patients, the glucose tolerance curve was found to be normal on a repeat test. In one instance, a diabetic type of curve followed an initial flat curve. In one group of patients, oral glucose administration produced flat venous blood values with low capillary blood glucose peaks. The maximum fall of serum inorganic phosphorus varied from 2 per cent to 20 per cent. In these instances, impaired glucose absorption may represent the mechanism involved.—C. R. SHUMAN

Further Observations on Infantile Idiopathic Hypoglycemosis. I. McQuarrie. *Am. J. Dis. Child.* 90: 591, 1955 (Soc. Trans).

During the past five years, 18 typical cases of infantile idiopathic hypoglycemosis have been studied. Many other single cases have come to light in widely-scattered communities throughout the United States and Canada. The principal features of the syndrome are as follows: (1) early age of onset (23 of 28 cases had first distinct symptoms before the age of 18 months); (2) absence of any characteristic physical stigmata; (3) symptoms which are varied and easily overlooked; (4) all special tests for liver, adrenocortical, thyroid, and pituitary insufficiency negative; (5) a strong familial tendency to spontaneous hypoglycemia (13 cases found in four

unrelated families in the author's series of 28 cases); (6) a natural tendency to recover or undergo marked amelioration with age; (7) uniformly favorable response to corticotropin (ACTH) therapy or large doses of cortisone or hydrocortisone.

Most cases cease to require hormone therapy after a few months' therapy. A few still require the hormone in minute doses over two years. In the latter, supplementation of corticotropin by pituitary growth hormone, thyrotropic hormone, gonadotropin, and lactogenic hormone separately or together showed no intensification or inhibition of the hyperglycemic effect of corticotropin.

The diagnosis of infantile idiopathic hypoglycemosis is simple when it exists and when it is tested for. This error of carbohydrate metabolism is far more common than diabetes mellitus among infants. Corticotropin therapy appears to be as efficacious in infantile idiopathic hypoglycemosis as insulin is in diabetes mellitus. —J. N. ETTELDORF

The so-called "browning reaction" developing in solutions of protein hydrolysates autoclaved in the presence of hexoses has been shown repeatedly to interfere with the nutritive value of the preparation.

Effects of Simultaneous or Prior Infusion of Sugars on the Fate of Infused Protein Hydrolysates. H. N. Christensen, P. B. Wilber, B. A. Coyne, and J. H. Fisher. *J. Clin. Investigation* 34: 86, 1955.

Glucose is usually included in amino acid solutions for intravenous infusion. In this interesting study the authors compared the effects of glucose and fructose on the fate of amino acids and peptides of protein hydrolysates in normal or convalescent subjects.

The presence of either sugar in certain commercial hydrolysates interferes with tissue utilization of the peptides, *if* the sugar and hydrolysate are autoclaved together. This interference is completely avoided if sugars are added to the hydrolysate just before infusion, or if the sugars are infused in advance of the hydrolysate.

There was a small advantage to fructose over glucose in that fructose did not interfere as much, and this is ascribed to the more rapid utilization of fructose. It is concluded that substances which interfere with peptide utilization are formed during autoclaving by an interaction between the sugar and unknown constituents of the hydrolysate.—S. O. WAIFE

For those who consider lactic acid to be one of the final products of anaerobic glycolysis which returns to the liver to undergo glycogenesis in accordance with the Cori cycle, the following report may be somewhat surprising.

Metabolism of Lactic Acid in the Intact Rabbit. D. R. Drury and A. N. Wick. *Am. J. Physiol.* 184: 304, 1956.

The metabolism of the lactic acid was studied in normal intact rabbits making use of C labeled L (+) lactate. The circulating lactate is being used up and renewed at a rapid rate. The turnover time is about 30 minutes. Eighty to ninety per cent of the lactate is disposed of by direct oxidation. Only a small percentage can be accounted for as glucose, glycogen, and by the oxidation of these. Lactate that is produced in emergency states can serve as a quick fuel for vital tissues in these situations.—AUTHORS

Relatively little is known of intermediary metabolism in the course of acute infectious diseases. The following study presents one important aspect of this subject.

Glucose Oxidation by Normal and Virus-Infected Mice. B. V. Siegel and A. M. Hughes. *Am. J. Physiol.* 184: 356, 1956.

The oxidation of uniformly C-labeled glucose by normal mice and mice infected with strain MEF_1 poliomyelitis virus was determined in an apparatus designed to measure respiratory radioactivity excretion. The respiration of normal and virus-infected mice was found to be essentially the same over a 10-day period of infection, although the production of virus in the diseased animal during this time was considerable. It is concluded that the rate and extent of viral multiplication in poliomyelitis is without apparent effect on the rate and extent of glucose metabolism by the infected intact host.—AUTHORS

NEW STUDIES ON SERUM LIPIDS

The levels of serum lipids, their physical state, their transport and utilization, are all influenced by a wide variety of conditions. These involve not only dietary factors, including certain vitamins, but also several hormones, exercise, temperature, age, and various disease states. The significance of the lipids in the formation of energy in cellular metabolism is gaining increasing recognition in biochemical studies. At the same time, there is a rapidly expanding literature on the role of the lipids in the production of vascular degenerative conditions. Investigations on the circulating lipid fractions and conditions affecting them provide both direct and indirect information concerning their metabolic activities. Lactescence of serum has recently been attributed primarily to the neutral fat fraction. It is of considerable interest that emulsified fat infusions produced a "clearing" effect in serum similar to that previously described with the administration of heparin.

Effects of Intravenously Administered Fat on the Serum Lipoproteins. F. S. M. Herbst, W. F. Leven, and W. R. Waddell. *Science* 123: 843, 1956.

Electrophoretic analyses of serum were performed in eight normal human subjects and in an equal number of dogs before and after an intravenous infusion of emulsified fat. The material consisted of 50 g of cottonseed

oil (or 50 g of synthetic triolein) with added soybean phosphatide.

The changes in lipoproteins and globulins seen on paper electrophoresis were identical with those induced by the intravenous administration of heparin during alimentary hyperlipemia in normal subjects and in patients with idiopathic hyperlipemia.

Heparin apparently activates a lipoprotein lipase, known as "clearing factor." It is not known whether an infusion of fat emulsion acts by a similar or different mechanism.—S. O. WAIFE

Comparison of Fat Emulsion Clearing Activities of Postheparin Plasma and Pancreatic Lipase. C. Hollett and H. C. Meng. *Am. J. Physiol.* 184: 428, 1956.

Work has been carried out to compare the properties of the lipemia clearing factor of postheparin plasma and pancreatic lipase. It was found that both postheparin plasma and pancreatic lipase exhibited lipolytic activity and were capable of clearing the turbidity of neutral fat emulsion. Intravenous administration of pancreatic lipase was able to clear alimentary lipemia, and postlipase plasma was also capable of clearing the turbidity of neutral fat emulsion *in vitro*. However, the results indicated that the lipemia clearing factor of postheparin plasma was not identical with pancreatic lipase or serum lipase of pancreatic origin. No appreciable change in plasma lipase was observed following intravenous administration of heparin. It is suggested that the lipemia clearing factor of postheparin plasma might be a specific esterase which is capable of splitting the ester bonds of neutral fat of long chain fatty acids.—AUTHORS

Effect of Liver on Lipolysis by Normal and Postheparin Sera in the Rat. J. A. Spitzer and J. J. Spitzer. *Am. J. Physiol.* 185: 18, 1956.

Lipolysis by sera heparinized *in vivo* and by normal sera was studied after perfusion through isolated rat liver. The rate of clearing of an oil emulsion by serum containing clearing factor was decreased after perfusion through the liver. The extent of clearing was not always affected. Clearing factor activity was lessened by incubation with heparinase (prepared from rabbit livers). Normal rat serum exhibited consistent lipolytic activity following perfusion through the isolated liver. This activity was not due to clearing factor.—AUTHORS

The Relation of Neutral Fat to Lactescence of Serum. M. J. Albrink, E. B. Man, and J. P. Peters. *J. Clin. Investigation* 34: 147, 1955.

A quantitative study was made of the relationship between serum neutral fat and cloudy sera. Neutral fat was the only lipid which was consistently associated with lactescence, which invariably was present when neutral fat exceeded 20 meq/l. The insoluble material causing lactescence was composed chiefly of neutral fat, but also included considerable quantities of cholesterol and phospholipid.

From these ultracentrifugal studies on solubility the authors postulate that the primary defect in lactescence is in the removal of soluble neutral fat from serum. Neutral fat is probably delivered to the serum chiefly in the insoluble form but is early converted to the soluble state. A limitation exists as to the maximum quantity of soluble neutral fat in the serum. If a block exists in the removal of this material, more and more insoluble neutral fat would accumulate.

It is also possible that cholesterol and phospholipid are dissolved in the insoluble neutral fat particles. This might explain why the solubility of these substances was decreased when neutral fat increased—S. O. WAIFE

Among the hormones known to affect lipid metabolism are insulin, growth hormone, adrenal steroids, and thyroxine. Insulin is known to exert a lipogenic effect, while the utilization of lipids is enhanced by growth hormone and thyroxine. Because of sex differences in lipid-protein distribution and in the incidences of coronary atherosclerosis, the influence of the gonadal hormones upon lipid metabolism is being examined in several clinics. The following reports demonstrate the controversial nature of the results.

Influence of Gonadal Hormones on Protein-Lipid Relationships in Human Plasma. E. M. Russ, H. A. Eder, and D. P. Barr. *Am. J. Med. Sc.* 19: 4, 1955.

Estrogenic hormones in the form of estinyl estradiol, estrone sulfate, or diethylstilbestrol tend to correct the pathologic protein-lipid relationships in patients with myocardial infarction, primary hypercholesterolemic xanthomatosis, and nephrosis. In the latter two diseases, there was a perceptible improvement, while in many of the infarction group there was a restoration of normal patterns. The improvements noted consisted of an increase in alpha-lipoproteins with a corresponding decrease in beta-lipoproteins. There is a change in ratio of concentration of cholesterol to phospholipid in the beta group to values less than 1.00. Usually, there is a decrease in cholesterol and phospholipid concentrations and in the cholesterol/phospholipid ratio.

Methyl testosterone modifies the protein-lipid relationships in a manner opposite to that observed after estrogen administration. It increases the beta- and decreases the alpha-lipoproteins. When estrogenic and androgenic hormones are given simultaneously, the estrogenic effects are modified or obliterated. These findings may explain the relative immunity of young women to atherosclerosis and suggest that the action of estrogenic substances might be beneficial in patients with atherosclerosis. On the other hand, methyl testosterone may be detrimental. The side effects of estrogenic therapy make it unacceptable to many patients.—C. R. SHUMAN

Influence of Physiologic Doses of Sex Steroid Hormones on Serum Lipids and Lipoproteins in Humans. H. Engelberg and S. J. Glass. *Metabolism* 4: 298, 1955.

Physiologic doses of testosterone plus estrogen, progesterone, and progesterone plus estrogens produced no consistent change in serum lipids or low density lipoproteins. With testosterone alone there was a suggestive rise in standard S_f 0-12 lipoproteins; however, the number of patients observed was too small to be conclusive. It is emphasized that the doses of hormones used in the study were those usually prescribed clinically. Larger doses were avoided because of the undesirable side-effects, and reliable evidence could not be obtained as to the physiologic role of these hormones in lipid metabolism.—C. R. SHUMAN

The physiologic consequences of adrenalectomy are so dramatic that conclusions concerning the effect of this procedure upon lipid metabolism in isolated tissues are tenuous. One would anticipate an increased mobilization of fat to liver with steroid administration and would question the possibility of an increased turnover of lipid in this organ in the adrenalectomized animal.

Effect of Adrenalectomy on the Incorporation of Acetate into Fatty Acids, Cholesterol and Acetoacetic Acid by Rat Liver Slices. W. F. Perry and H. F. Bowen. *Am. J. Physiol.* 184: 59, 1956.

The incorporation of C-acetate into fatty acids, cholesterol, acetoacetic acid and CO_2 by liver slices of intact and adrenalectomized rats was studied, the slices being incubated in bicarbonate and phosphate buffers. It was found that in both buffer systems incorporation into fatty acids and cholesterol was depressed while incorporation into acetoacetic acid was unaffected by adrenalectomy. However, total acetoacetic acid formation by the slices tended to be higher in preparations from adrenalectomized animals. The amount of acetate carbon appearing as CO_2 was similar with slices from both types of animals. Bicarbonate was found to be a more favorable medium than PO_4 for fatty acid formation, while PO_4 was the more favorable medium for cholesterogenesis, though the differences between adrenalectomized and intact animals persisted in either buffer. Forced feeding with glucose increased the incorporation of acetate into fat and cholesterol in both buffer systems in adrenalectomized as well as in intact animals. However, the adrenalectomized preparation still incorporated acetate to a lesser extent than the controls. It was concluded that while the depressed incorporation of acetate into fatty acid and cholesterol by adrenalectomized liver slices was consistent with a depressed synthesis of these lipids, there was also the possibility that it reflected an increased turnover of lipids in the liver of the adrenalectomized animal—AUTHORS

Role of Hypophysis and Adrenals in Fatty Infiltration of Liver Resulting from Acute Ethanol Intoxication. S. Mallov and J. L. Bloch. *Am. J. Physiol.* 184: 29, 1956.

Acute ethanol intoxication was found to promote the fatty infiltration of liver in rats. The liver lipid concentrations gradually rose to peak values, then slowly returned to normal. The duration of the fatty infiltration, and the peak liver lipid values obtained, were functions of the dose of ethanol administered. Female rats showed a more severe fatty infiltration than did males, under the same conditions. The prior administration of large quantities of choline reduced the intensity of the fatty infiltration provoked by the ethanol. In contrast to intact animals, neither adrenalectomized nor hypophysectomized rats showed an accumulation of liver lipids as a result of acute ethanol intoxication. Adrenalectomized rats maintained on cortisone, and adrenal demedullated rats, however, showed the same liver lipid response to ethanol as did intact rats. Rats chronically intoxicated for a period of 30 days exhibited hypertrophy of the adrenals. Acute intoxication produced by isopropanol administration also resulted in the accumulation of liver lipid. It is suggested that ethanol intoxication may cause the mobilization of fat from the depots to the liver, and that pituitary and adrenal cortical hormones are involved in the mechanism of this mobilization.—AUTHORS

The reduction of serum lipid levels in association with the ingestion of vegetable fats has been ascribed to changes in the gastrointestinal absorption of the esterified fatty acids derived from these sources. The practical aspects of this type of investigation in devising a possible approach to the problem of atherosclerosis are apparent.

The Effects of Certain Vegetable and Animal Fats on the Plasma Lipids of Humans. J. M. R. Beveridge, W. F. Connell, G. A. Mayer, J. B. Firstbrook, and M. S. DeWolfe. *J. Nutrition* 56: 311, 1955.

The purpose of this investigation was to find if there is an association of high plasma lipid levels and a high incidence of atherosclerosis which has been noted by many investigators.

Five apparently healthy male subjects, aged 33 to 41 years, consumed alternately mixed "free-choice" diets and homogenized "formula" diets. The latter, of accurately known composition, varied both in cholesterol content and in the amount and type of fat. Blood samples were taken throughout the study and the plasma was analyzed for total and free cholesterol and phospholipid.

Diets containing vegetable fat, comprising either 28.4 or 58.5 per cent of total calories, with or without supplementary cholesterol, led to decreases of similar magnitude in plasma lipid levels relative to the levels found on the antecedent mixed "free-choice" diets. When animal fat, in the form of butter, was given to

provide 58.5 per cent of calories, there was an actual increase in lipid levels on the fourth and seventh days, followed by a return to a level slightly below that recorded at the beginning of this dietary period.

Under the conditions of this study, there was a highly significant statistical difference between the effects of vegetable fat and animal fat on the blood lipids. A hypothesis has been postulated to explain why a high dietary level of vegetable fat in a non-vegetarian diet of mixed foodstuffs causes an increase in plasma lipids, whereas it has no such effect when included in a homogenized simple formula diet as the sole source of fat.—B. SURE

Relation of Dietary Fat to the Absorption and Elimination of Exogenous and Endogenous Cholesterol. T.-M. Lin, E. Karvinen, and A. C. Ivy. *Am. J. Physiol.* 183: 86, 1955.

Male rats (200-220 g.) were used as test objects. One gram of fat and fifty milligrams of cholesterol were fed daily. Oleic acid decreased endogenous elimination of cholesterol. Tallow had a similar but much smaller action. However, corn oil and triolein increased the elimination of cholesterol. Oleic acid was the most effective agent which increased absorption of ingested cholesterol. Tallow and corn oil were less effective. The action of triolein was insignificant. Indeed, if tripalmitin or palmitic acid were fed, the absorption of cholesterol was decreased. Except for triolein, the absorption of cholesterol varied directly with the per cent utilization of fat ingested along with the cholesterol. —M. J. OPPENHEIMER

Influence of Dietary Fat on Incidence of Alloxan Diabetes in Growing Rats. C. Nieman. *Am. J. Physiol.* 181: 183, 1955.

Rats were made diabetic with alloxan and fed an adequate diet with 10 to 20 per cent fat. The effect of alloxan was influenced by the nature of the dietary fat. Butter fat protected the animals to a greater extent than did peanut oil. The greater content of saturated fatty acids in butter fat is considered to be important in the protection furnished. It was also observed that urinary riboflavin was greatly increased in alloxan diabetes. Whether this was the result of "washing out" or due to a defect in intermediary metabolism remains to be studied.—M. J. OPPENHEIMER

Inasmuch as certain features of atherosclerosis have been noted in coronary vessels of male infants, and because there is scant information concerning serum lipid levels and factors influencing them at this age, studies such as the following are of equal importance as the many similar reports dealing with aging individuals.

Studies on Serum Lipids and Lipoprotein in Infancy and Childhood. S. Rafstedt. Dissertation, University of Lund, Sweden, 1955.

Relatively little is known about serum lipids in infants and children. In this dissertation from the University of Lund, Sweden, the author reports his interesting findings, which were determined by micro-analysis. Serum obtained from umbilical cord blood contained much less lipid, total and free cholesterol, and phospholipid than normal adult serum. Thus the mean total cholesterol in cord blood was 74 mg/100 ml. The α-lipoproteins were increased, the β-lipoproteins decreased (43:33 per cent in umbilical cord blood, and 30:50 per cent in adult blood).

There is a rapid increase in serum lipids during the first 12 hours of life, and this is attributed, in part, to dehydration. By the fourth day the serum lipids reached levels 80 to 90 per cent higher than at birth. The increase in β-lipoproteins was most noticeable. Successive analyses from the same infants during the first year showed some fluctuation and a slight tendency to increase by the end of the year. The values for newborns delivered by Caesarian section did not differ from those delivered normally. Neither did the lipids and lipoproteins of premature infants differ from those of full-term babies.

In infants on a fat-poor diet, as well as in those on a sugar-amino acid-synthetic diet, the serum lipids and lipoproteins did not increase as rapidly in the first few days of life as in infants fed an ordinary diet. In infants fed carbohydrate only (no milk) during the first few days the serum lipids did not change, nor did any change occur in lipoprotein distribution. However, when these newborns received an ordinary feeding, the serum lipids and lipoproteins promptly rose to values found in those brought up on mixed (milk) feeding from birth. The data in this report are well presented, instructive, and valuable.—S. O. WAIFE

The Serum Lipoproteins in Slight Malnutrition. C.-B. Laurell. *Scandinav. J. Clin. & Lab. Investigation* 7: 257, 1955.

Lipoproteins were studied in 27 persons who had had a partial gastrectomy within the previous 5 years. The results were compared with those from samples obtained from 50 blood donors. According to the author, in "slight malnutrition the values for total lipids, phospholipids and β-lipoprotein decrease," but the concentration of α-lipoprotein is unchanged.

Unfortunately, we are not told much about the "slight malnutrition" except that some patients felt well and others lost weight. In addition, according to the method described the albumin fraction is not clearly separated from α-lipoproteins.—S. O. WAIFE

ITEMS OF GENERAL INTEREST

Tube Feeding with Natural Foods in Elderly Patients. J. Barron and L. S. Fallis. *J. Am. Geriatrics Soc.* 4: 400, 1956.

The problem of providing adequate calories to elderly patients is a common and serious postoperative problem. The authors, from the Henry Ford Hospital,

Detroit, suggest that this can be accomplished by tube feeding of natural foods. A small nonirritating plastic tube is passed into the upper gastrointestinal tract and kept in place for an indefinite period of time. They point out that a liquid mixture of natural foods can be made using a Waring blendor. The new innovation is to use a small pump to force the mixture down the tube rather than by a gravity drip. The mixture is given over an 8- to 10-hour period rather than all at once. In this way, vomiting and diarrhea are avoided.

Although not new, this variation of tube feeding may be of very definite benefit in providing adequate calories for the elderly postoperative patient. It seems possible that this may be of psychologic benefit also, because the patient feels that something "definite" is being done for him.—K. R. CRISPELL

Failure of Excess Minerals in the Diet to Accelerate the Healing of Experimental Fractures. J. A. Key and R. T. Odell. *J. Bone & Joint Surg.* 37: 37, 1955.

Does the addition of minerals to an already adequate diet influence the healing of fractures? Experiments reported on 130 rats (half of which were supplemented with a mixture of mineral salts including $MgSO_4$, $Ca(PO_4)_2$, $Mg(Cl)_2$, etc.) reveal that no significant changes in type or rate of healing of experimental fractures were noted. The weight gain of the experimental group was 9.6 per cent greater than the adequately fed control group.

While human implications from such experiments are risky, the authors themselves point out that whereas the control animals were on an "optimum" diet, "the average person who suffers a fracture may be on an adequate, but considerably less than optimum, mineral intake."

This reviewer believes the whole subject of mineral-protein nutrition in fractures deserves more study. The implications, particularly to the elderly, are obvious.—S. O. WAIFE

Accelerated Storage Tests for Dehydrated Vegetables. E. G. B. Gooding and R. B. Duckworth. *Nature* 177: 897, 1956.

When dehydrated vegetables are stored at high temperatures they eventually become unacceptable, usually due to the development of brown pigments, but it is almost impossible to predict their storage life without testing. Normally, tests are carried out at 37° C, but this may involve long delays.

The browning was measured both by extraction of the pigment with ethanol and by visual assessment, and it was shown that browning took place at thirty times the speed at 55° C compared to 37° C. That is, by employing the higher temperature, tests can be made in days rather than months.—F. E. HYTTEN

Man's Choice of Food. J. Yudkin. *Lancet* 1: 645, 1956.

In this lecture, Professor Yudkin briefly discusses the factors determining the choice of nutrients. These are divided into three main sections: (1) factors of availability, (2) social factors, and (3) physiologic factors.

Under the factors of availability are discussed geography—its influence has been greatly modified by modern transport; season—again influenced by transport and by newer methods of food preservation; economics—the change in the composition of diets which depend largely on the available money; and other factors such as new foods made available by advances in technology and limitations on the use of some foods dictated by limitations of cooking fuel.

Among social factors, religious and social factors, nutritional education, and advertising by food firms are briefly discussed.

Under the heading of physiologic factors, palatability, allergy, and the use of therapeutic diets are mentioned, and the question of choice to fill a nutritional need is discussed in some detail. The experiments in which children have been shown to eat a well-balanced diet when given a free choice are thought to be invalid because only nutritionally desirable foods were offered. The fact that the Chinese have no instinct to avoid beriberi when they eat polished rice is one of a number of examples showing that the instinct to choose a good diet is far from proved. Animal experiments suggest that the ability to select a suitable diet depends on such things as age, heredity, and pregnancy, or on whether the unsuitable constituents provide rapid evidence of harm. "Instinctive" choice is often influenced by learning rather than by true instinct or by a feeling of well-being engendered by the food. Moreover, a good diet might be bypassed for a worthless but more palatable one.

A "hypothesis of satiety" is developed to show that an animal may be more satisfied and more comfortable by eating a variety of foods rather than by concentrating on one.—F. E. HYTTEN

Suckling Rats Injected with Beta-Amino-Propionitrile (Lathyrus Factor). J. J. Clemmons and D. M. Angevine. *Fed. Proc.* 11: 512, 1956.

Weanling rats were injected with 0.1–0.3 ml of a 2 per cent solution of β-amino-propionitrile, the toxic "lathyrus-factor" present in sweet peas, *Lathyrus odoratus*. Multiple fractures and osteoporosis of the long bones developed within 72 hours. Organic matrix was decreased and the osteoblasts had degenerated. The lesions were comparable to those of osteogenesis imperfecta in man.—M. SILBERBERG

Favism in an English-born Child. G. Discombe and W. Mestitz. *Brit. M. J.* 1: 1023, 1956.

A case is described of a $2^1/_2$-year-old girl who had a sudden hemolytic episode after a meal of broad beans.

Both parents were of Mesopotamian origin, but in neither of their families was there any history of hemolytic anemia.—F. E. HYTTEN

Intestinal Excretion of Cholesterol and Total Lipids by the Nephrotic Rat. S. O. Byers, R. H. Rosenman, and M. Friedman. *Am. J. Physiol.* 182: 73, 1955.

Rats were made nephrotic by the injection of potent rabbit anti-rat kidney serum. Observations on the intestinal excretion of cholesterol and total lipids were carried out on these test animals and were then compared to a group of controls. The results were negative in that the fecal excretion of cholesterol and fat was the same in both control and experimental groups. The hypercholesteremia and hyperlipemia of experimental nephrosis cannot be attributed to diminished intestinal excretion.—M. J. OPPENHEIMER

Lipoprotein Studies in Atherosclerotic and Lipemic Individuals by Means of Paper Electrophoresis. S. P. Gottfried, R. H., Pope, N. H. Friedman, I. B. Akerson, and S. DiMauro. *Am. J. Med. Sc.* 229: 34, 1955.

Total serum lipids, total cholesterol, and alpha- and beta-lipoprotein determinations were performed on 8 patients with arteriosclerotic disease, 39 control subjects, and 17 subjects with lipemia; both sexes were represented with an age range of 20 to 55 years. Among the normal subjects, the beta-lipoproteins were found to be higher in men in their twenties than in women of the same age. No variations were observed in the alpha-lipoprotein greater than that seen in the controls. These gradually decreased with the passage of time. There appears to be no apparent relationship between lipids, cholesterol, and the lipoproteins. Of the 8 atherosclerotic patients, all showed at least one elevated serum lipid or total cholesterol or both. In the lipemic group, an elevated beta-lipoprotein was obtained in about 50 per cent of those studied.—C. R. SHUMAN

Instability of Milk Due to a High Content of Calcium Ions. J. Boogaert. *Nature* 174: 884, 1954.

A condition of milk whereby it flocculates after boiling or even after short storage, and known as "the Utrecht abnormality of milk," is now rare in the Netherlands, although it caused serious concern in the 1930's. No unusual chemical properties were then discovered, but in a few recent examples of the abnormality a high content of calcium ions has been found. In four samples reported, the calcium ion content ranged from 14.8 to 27 mg per 100 ml.—F. E. HYTTEN

A Relationship between Body Fat and Plasma Cholinesterase. W. T. C. Berry, P. J. Cowin, and D. R. Davies. *Brit. J. Nutrition* 8: 79, 1954.

The aim of this study was to determine whether there was any relationship between body fat and plasma cholinesterase. Measurements of surface fat and plasma cholinesterase have been carried out on 345 males. Surface fat was measured as skinfold thickness at five sites. Plasma cholinesterase was estimated from samples of blood collected upon filter paper. A highly significant positive correlation was found between the surface fat and plasma cholinesterase for each of the groups tested. Body weight only slightly influenced the relationship, which, on the limited evidence available, was not in any way affected by calorie intake.—B. SURE

Influence of Potassium Deprivation and Adrenalectomy on Potassium Concentration of the Myocardium. S. St. George, S. C. Freed, R. H. Rosenman, and S. Winderman. *Am. J. Physiol.* 181: 550, 1955.

Five-week-old male rats were fed a synthetic diet which contained 0.006 per cent potassium and 0.6 per cent sodium. The latter is a normal amount. On this regime potassium depletion was well advanced in five weeks. Rats were maintained on this diet for seven weeks but half of them had a bilateral adrenalectomy at the end of five weeks. All animals were sacrificed at the end of seven weeks. After adrenalectomy both controls and those on the K-deficient diet were observed to have an elevated plasma potassium. Skeletal muscle potassium was increased in adrenalectomized rats on K-deficient diets but not in controls. Neither experimental nor control adrenalectomized animals were demonstrated to have any change in myocardial potassium. The myocardium may have more "bound" and hence nonexchangeable potassium than skeletal muscle does.—M. J. OPPENHEIMER

An Apparently Homogeneous Substance with Intrinsic-Factor Activity Associated with Cell Particles from Human Stomach. J. R. P. O'Brien, W. H. Taylor, A. L. Turnbull, and L. J. Witts. *Lancet* 1: 847, 1955.

A substance has been isolated from the human stomach which will promote the absorption of 32 per cent of radioactive vitamin B_{12} in a dose of 10 mg. Its chemical separation is described. It appears to be a single substance with a molecular weight of about 40,000 and is associated in the cell with the nuclei, mitochondria, or microsomes. It is less active than intrinsic factor prepared by other workers, is of higher molecular weight, and is of pale yellow color. It is suggested that it may be a precursor of intrinsic factor.—F. E. HYTTEN

Does Milk Protect Infants Against Malaria? M. J. Colbourne. *Trans. Roy. Soc. Trop. Med. & Hyg.* 50: 82, 1956.

It has been shown that a purely milk diet protects rats against experimental plasmodia infection, and that *p*-aminobenzoic acid prevents this protection. In this study, 55 infants in Accra, Gold Coast, were followed twice weekly from birth to age 6 months. The results, only partially substantiate this observation. Thus, of 17 infants who reached 6 months of age while receiving *p*-aminobenzoic acid (PABA) supplements, 12 (71 per cent) developed malaria; of 22 controls, half (11) developed malaria. The results show that up to the age of three months the yeast supplements (containing PABA) made little difference in the chance of acquiring

malaria, but in the 3- to 6-month age group the babies that had received yeast supplements became more susceptible to infection. This article also discusses other factors which may have been operative.—S. O. WAIFE

The Failure of Acetylation in Diabetic Coma. F. Navazio and N. Siliprandi. *Lancet* 2: 1174, 1955.

Human blood is normally able to acetylate *p*-aminobenzoic acid and sulfanilamide *in vitro*. Data are presented to show that while acetylation occurs normally in (presumably controlled) diabetics, it does not occur in the blood from diabetics in coma.—F. E. HYTTEN

Local Cutaneous Response to Nicotinic Acid and Esters as a Diagnostic Aid for Rheumatoid Arthritis. P. Leifer, and R. C. Batterman. *Am. J. Med. Sc.* 230: 657, 1955.

The application of esters of nicotinic acid to the skin of patients with rheumatoid arthritis and acute rheumatic fever has been reported to produce a local erythematous response indicative of activity of the disease. This study was initiated to evaluate this procedure in patients with rheumatoid arthritis and to examine the action of various derivatives of nicotinic acid. It was found that approximately 80 per cent of the subjects tested developed a reaction of localized hyperemia or edema or both, regardless of their rheumatic condition. The skin response was the same for patients with and without rheumatoid arthritis. No correlation could be established between the skin reaction and the clinical status of the patient, the sedimentation rates, or the C-reactive protein reactions.—C. R. SHUMAN

Plasma Phospholipide Deposition and Aortic Phospholipide Synthesis in Experimental Atherosclerosis. M. L. Shore, D. B. Zilversmit, and R. F. Ackerman. *Am. J. Physiol.* 181: 527, 1955.

New Zealand rabbits were maintained for five months on diets supplemented with cholesterol dissolved in vegetable fat. These animals and a control series were then injected intravenously with native plasma phospholipides which were labeled with P^{32}. The resulting atheromatous thoracic aortas were examined for phospholipides by extraction with alcohol-ether and petroleum ether. Deposition of plasma phospholipides could account for less than one-tenth of that detected in the atheromatous thoracic aortas. This emphasizes that most of the phospholipide in experimental atheromatosis is synthesized locally in the tissue of the aortas. —M. J. OPPENHEIMER

Nutrition in Tuberculosis. S. M. Farber, R. H. L. Wilson, and N. L. Hooper. *Journal-Lancet* 76: 100, 1956.

After briefly reviewing the various concepts of nutrition in tuberculosis the authors conclude that by and large there is less concern now with this problem than has been the case in past centuries. The great advances in chemotherapy and surgery have drawn attention away from the role of diet. It is also true that our "knowledge" on the subject is more apparent than real because of the vast difference between what is ordered and what is actually eaten in a tuberculosis hospital. The assumption that nutrition poses no special problem now is premature, because actually very little work has been done on the relationship of actual food intake and clinical response.—S. O. WAIFE

THE AMERICAN JOURNAL OF Clinical Nutrition

CONTENTS OF VOLUME 4

January-February 1956

ESTIMATION OF CALORIC INTAKE FROM DIETARY HISTORIES AMONG POPULATION GROUPS	Frederick H. Epstein, Ruth Carol, and Rita Simpson	1
RELATIONS BETWEEN DIET AND ATHEROSCLEROSIS AMONG A WORKING POPULATION OF DIFFERENT ETHNIC ORIGINS	Frederick H. Epstein, Rita Simpson, and Ernst P. Boas	10
THE DEGREE OF MASCULINE DIFFERENTIATION OF OBESITIES: A FACTOR DETERMINING PREDISPOSITION TO DIABETES, ATHEROSCLEROSIS, GOUT, AND URIC CALCULOUS DISEASE	Jean Vague	20
ESTIMATION OF THE PROPORTION OF FAT IN THE BODY BY MEASUREMENT OF SKIN-FOLD THICKNESS	D. A. W. Edwards	35
RELATIVE IMPORTANCE OF INACTIVITY AND OVEREATING IN THE ENERGY BALANCE OF OBESE HIGH SCHOOL GIRLS	Mary Louise Johnson, Bertha S. Burke, and J. Mayer	37
METABOLISM IN SURGICAL PATIENTS. I. NITROGEN METABOLISM IN TOTALLY GASTRECTOMIZED PATIENTS	Morton K. Schwartz, Oscar Bodansky, and Henry T. Randall	45
METABOLISM IN SURGICAL PATIENTS. II. FAT AND MINERAL METABOLISM IN TOTALLY GASTRECTOMIZED PATIENTS	Morton K. Schwartz, Oscar Bodansky, and Henry T. Randall	51
CLINICAL USE OF SORBITOL AS A SWEETENING AGENT IN DIABETES MELLITUS	Charles R. Shuman, Robert L. Kemp, Richard Coyne, and Michael G. Wohl	61
THE DISTRIBUTION OF VITAMIN A IN CELLS OF NORMAL AND PATHOLOGIC HUMAN LIVERS	R. F. Krause and P. L. Sanders	68
THE EFFECT OF NUTRITIONAL DEFICIENCY ON THE PITRESSIN-INACTIVATING ABILITY OF THE LIVER	K. Guggenheim	71
LETTERS TO THE EDITOR: THE CLAIM OF "LACK OF EFFECT OF HIGH FAT INTAKE ON SERUM LIPID LEVELS"	Ancel Keys	74
COMMENT	George V. Mann	76
NUTRITION NEWS		78
NUTRITIONAL QUOTES		80
REVIEWS OF RECENT BOOKS		81
ABSTRACTS OF CURRENT LITERATURE: NUTRITION SURVEYS; PEDIATRIC NUTRITION; STEATORRHEA; NUTRITION AND SMALL INTESTINE FUNCTION; ANEMIA; GROWTH-PROMOTING GACTORS; VITAMIN E; METABOLIC ASPECTS OF STRESS; ITEMS OF GENERAL INTEREST		83

March-April 1956

THE EFFECTS OF NUTRITIONAL DEFICIENCY ON THE HEART: A REVIEW	Richard H. Follis, Jr.	107
SERUM CHOLESTEROL CONCENTRATION IN NEW-BORN AFRICAN AND EUROPEAN INFANTS AND THEIR MOTHERS	I. Bersohn and S. Wayburne	117
INTESTINAL ABSORPTION AND HEPATIC UPTAKE OF RADIOACTIVE VITAMIN B_{12} IN VARIOUS AGE GROUPS AND THE EFFECT OF INTRINSIC FACTOR PREPARATIONS	George B. Jerzy Glass, A. Allen Goldbloom, Linn J. Boyd, Roger Laughton, Sidney Rosen, and Marilyn Rich	124
APPLICATIONS OF THE URINARY TRACER TEST (OF SCHILLING) AS AN INDEX OF VITAMIN B_{12} ABSORPTION	Edward H. Reisner, Jr., Jack P. Gilbert, Charles Rosenblum, and Mary C. Morgan	134
THE URINARY EXCRETION TEST FOR ABSORPTION OF VITAMIN B_{12}. I. REPRODUCIBILITY OF RESULTS AND AGEWISE VARIATION	Bacon F. Chow, Jack P. Gilbert, Kunio Okuda, and Charles Rosenblum	142

THE URINARY EXCRETION TEST FOR ABSORPTION OF VITAMIN B_{12}. II. EFFECT OF CRUDE AND PURIFIED INTRINSIC FACTOR PREPARATION — Bacon F. Chow, William L. Williams, Kunio Okuda, and Ralph Grasbeck 147

STUDIES OF NIACIN REQUIREMENT IN MAN. III. COMPARATIVE EFFECTS OF DIETS CONTAINING LIME-TREATED AND UNTREATED CORN IN THE PRODUCTION OF EXPERIMENTAL PELLAGRA — Grace A. Goldsmith, Janis Gibbens, Walter G. Unglaub, and O. Neal Miller. 151

LYSINE AND TRYPTOPHAN CONTENT OF PROTEINS AND THEIR UTILIZATION FOR HUMAN GROWTH — Anthony A. Albanese, Reginald A. Higgons, Gertrude M. Hyde, and Louise Orto 161

RELATION BETWEEN CALORIC INTAKE, BODY WEIGHT, AND PHYSICAL WORK: STUDIES IN AN INDUSTRIAL MALE POPULATION IN WEST BENGAL — Jean Mayer, Purnima Roy, and Kamakhya Prasad Mitra 169

EDITORIALS: ARE THE OBESE METABOLICALLY DIFFERENT? — S. O. Waife 176

EUTROPHY — S. O. Waife 176

DIET THERAPY: DEVELOPMENT AND ROLE OF A FOOD CLINIC — Clare E. Forbes 178

NUTRITION NEWS 181

NUTRITION BRIEFS 182

NUTRITIONAL QUOTES 183

REVIEWS OF RECENT BOOKS 185

ABSTRACTS OF CURRENT LITERATURE: PROTEIN NUTRITION; THINNESS AND UNDERNUTRITION; SODIUM AND CARDIOVASCULAR DISEASE; RICKETS, VITAMIN D, AND CALCIUM; THIAMINE METABOLISM; FLUORINE—ESSENTIAL TRACE ELEMENT?; IODINE DEFICIENCY; ITEMS OF GENERAL INTEREST 188

May-June 1956

THE CRITICAL WORLD FOOD SITUATION — Barnett Sure 211

THE EFFECTS OF SUPPLEMENTARY CALORIES ON NITROGEN STORAGE AT HIGH INTAKES OF PROTEIN IN PATIENTS WITH CHRONIC LIVER DISEASE — Irvin C. Plough, Frank L. Iber, Margaret E. Shipman, and Thomas C. Chalmers .. 224

THE PREVALENCE AND INCIDENCE OF OBESITY IN A CROSS-SECTION OF ELEMENTARY AND SECONDARY SCHOOL CHILDREN — Mary Louise Johnson, Bertha S. Burke, and J. Mayer 231

DIETARY INTAKE AND SOCIAL CHARACTERISTICS — Jean K. Boek 239

HIGH FLUORIDE CONTENT OF TEETH FROM COMMUNITIES WITH LOW FLUORIDE WATER SUPPLIES — James H. Shaw, Om P. Gupta, and Margaret E. Meyer 246

METHODS FOR PREPARING DIETS LOW IN SODIUM AND HIGH IN PROTEIN — Sherman Beychok, Arthur Katchman, Harry Baron, and Israel S. Kleiner 254

NUTRITIONAL STATUS OF SELECTED ADOLESCENT CHILDREN — Margaret McGregor Hard and Nettie C. Esselbaugh 261

OBSERVATIONS ON THE URINARY EXCRETION OF THIOCTIC ACID — E. L. Patterson, H. P. Broquist, M. H. von Saltza, A. Albrecht, E. L. R. Stokstad, and T. H. Jukes 269

EFFECT OF FOOD INTAKE ON AMINO ACIDS IN HUMAN PLASMA — E. Staten Wynne and Cora L. Cott 275

THE EFFECT OF ORAL DEXTRAN ON BLOOD GLUCOSE — Robert H. Joelson 279

DENTAL SURVEY OF SELECTED THAI CHILDREN: NUTRITIONAL OBSERVATIONS — Od Kridakara, Rith Boozayaangool, Isra Yuktananda, and J. F. Volker 280

LETTERS TO THE EDITOR: EFFECT OF A SYNTHETIC TRIGLYCERIDE ON LIPID METABOLISM — Laurance W. Kinsell, Roger W. Friskey, George D. Michaels, and Frederick R. Brown 285

THE ROLE OF AMINO ACIDS IN KWASHIORKOR — J. F. Brock, J. D. L. Hansen, and E. E. Howe 286

DIET THERAPY: FIBER IN THE DIET — Corinne H. Robinson 288

OBITUARY: HAROLD RUSSELL SANDSTEAD 291

NUTRITION NEWS 292

NUTRITION BRIEFS 293

NUTRITIONAL QUOTES 294

REVIEWS OF RECENT BOOKS 295

ABSTRACTS OF CURRENT LITERATURE: DIETARY MANAGEMENT OF PEPTIC ULCER; KWASHIORKOR AND PROTEIN MALNUTRITION; ALCOHOL AND NUTRITION; MILK AND LACTATION; VITAMIN C: INTAKE, SERUM LEVELS, ACTIONS; ITEMS OF GENERAL INTEREST 297

July-August 1956

SYMPOSIUM ON THE ROLE OF SOME OF THE NEWER VITAMINS IN HUMAN METABOLISM AND NUTRITION: INTRODUCTION — William J. Darby 309

IN MEMORIAM/DR. JAMES FLEECE RINEHART, 1901–1955 — Louis D. Greenberg 311

THE HISTORY OF VITAMIN B_6 — Paul György 313

VITAMIN B_6 DEFICIENCY IN THE RHESUS MONKEY WITH PARTICULAR REFERENCE TO THE OCCURRENCE OF ATHEROCSLEROSIS, DENTAL CARIES, AND HEPATIC CIRRHOSIS — James F. Rinehart and Louis D. Greenberg 318

NEUROCHEMICAL ASPECTS OF PYRIDOXINE METABOLISM AND FUNCTION — Donald B. Tower 329

THE NEUROPATHOLOGY OF EXPERIMENTAL VITAMIN B_6 DEFICIENCY IN MONKEYS — Maurice Victor and Raymond D. Adams. 346

EFFECTS OF VITAMIN B_6 ON THE CENTRAL NERVOUS ACTIVITY IN CHILDHOOD — David Baird Coursin 354

SOME METABOLIC EFFECTS OF VITAMIN B_6 *in vivo* — E. W. McHenry 364

EVIDENCE FOR ABNORMAL VITAMIN B_6 METABOLISM IN PREGNANCY AND VARIOUS DISEASE STATES — M. Wachstein 369

THE METABOLISM OF VITAMIN B_6 IN HUMAN BEINGS — Richard W. Vilter 378

NUTRITIONAL MUSCULAR DYSTROPHY IN MONKEYS RECEIVING A DIET DEFICIENT IN BOTH VITAMINS B_6 AND E — Paul L. Day and James S. Dinning 386

SOME STUDIES OF TOCOPHEROL IN INFANTS AND CHILDREN — Harry H. Gordon and Harold M. Nitowsky 391

SOME STUDIES OF TOCOPHEROL DEFICIENCY IN INFANTS AND CHILDREN. III. RELATION OF BLOOD CATALASE ACTIVITY AND OTHER FACTORS TO HEMOLYSIS OF ERYTHROCYTES IN HYDROGEN PEROXIDE — Harold M. Nitowsky and J. Tyson Tildon 397

ALPHA-TOCOHYDROQUINONE AND MUSCLE DYSTROPHY — Philip L. Harris and Karl E. Mason 402

EFFECTS OF LIMITED TOCOPHEROL INTAKE IN MAN WITH RELATIONSHIPS TO ERYTHROCYTE HEMOLYSIS AND LIPID OXIDATIONS — M. K. Horwitt, C. C. Harvey, G. D. Duncan, and W. C. Wilson 408

STUDIES OF PANTOTHENIC ACID METABOLISM — Robert Lubin, Kate A. Daum, and William B. Bean 420

EFFECT OF AN ELIXIR ON THE ABSORPTION OF VITAMIN B_{12} BY HEALTHY YOUNG AND OLD SUBJECTS — Bacon F. Chow, Andrew Horonick, and Kunio Okuda 434

VITAMIN B_{12} SERUM LEVEL AND PREGNANCY — Kunio Okuda, Andre E. Helliger, and Bacon F. Chow 440

NUTRITION NEWS 444

REVIEWS OF RECENT BOOKS 446

ABSTRACTS OF CURRENT LITERATURE: ARTERIOSCLEROSIS: NUTRITIONAL CONSIDERATIONS; NUTRITION AND PREGNANCY; IRON METABOLISM; THE ACTION OF VITAMIN K; THE PANCREAS AND LIPIDS; PERNICIOUS ANEMIA AND VITAMIN B_{12}; ITEMS OF GENERAL INTEREST 447

September-October 1956

SYMPOSIUM ON NUTRITION AND THE KIDNEY: INTRODUCTION — Robert M. Kark 463

THE EFFECTS OF DIET ON RENAL FUNCTION IN HEALTHY MEN — Frederick Sargent and Robert E. Johnson 466

NUTRITIONAL ASPECTS OF ACUTE GLOMERULONEPHRITIS — Hyman J. Zimmerman 482

DIETARY TREATMENT IN ACUTE ANURIA — K. G. Lowe and H. Valtin 486

NUTRITION IN CHRONIC RENAL FAILURE — Arthur J. Merrill 497

NUTRITION AND THE NEPHROTIC SYNDROME IN ADULTS — John R. Squire — 509

KALIOPENIC NEPHROPATHY — Jerome W. Conn and Robert D. Johnson. — 523

RENAL FUNCTION IN SCURVY — L. Eales — 529

RENAL LESIONS IN KWASHIORKOR — J. N. P. Davies — 539

OBSERVATIONS ON THE RENAL DEFENSE OF BODY COMPOSITION IN CHILDREN — Jack Metcoff — 543

CALCIUM AND THE KIDNEY — Daniel S. Kushner — 561

EDITORIALS: A WELL-DESERVED TRIBUTE — S. O. Waife — 580
ROBERT R. WILLIAMS: A TRIBUTE — Norman Jolliffe — 580
TRIBUTE TO DR. ROBERT R. WILLIAMS — William H. Sebrell — 582

NUTRITION NEWS — 585

NUTRITION BRIEFS — 586

NUTRITIONAL QUOTES — 587

REVIEWS OF RECENT BOOKS — 589

ABSTRACTS OF CURRENT LITERATURE: NIACIN REQUIREMENTS AND METABOLISM; NUTRITIONAL PROBLEMS INVOLVING THE GASTROINTESTINAL TRACT — 591

November-December 1956

VITAMIN E. DEFICIENCY IN MAN: BIOCHEMICAL EVIDENCE IN A PATIENT WITH XANTHOMATOUS BILIARY CIRRHOSIS — Calvin W. Woodruff — 597

HYPERVITAMINOSIS A. EXPERIMENTAL INDUCTION IN THE HUMAN SUBJECT — Robert W. Hillman — 603

ABSORPTION OF IRON FROM THE GASTROINTESTINAL TRACT — Elaine D. Henley, W. N. Christenson, William J. Grace, and Harold G. Wolff — 609

PYRUVATE METABOLISM IN OBESITY — A. T. Miller, Jr., and Barbara M. Thomas — 619

THE CARE AND NUTRITION OF A PATIENT IN PROLONGED COMA — Ralph L. Hopp, W. J. A. Ford, and S. J. O'Connor — 625

THE NUTRITION OF THE ISOLATED VERTEBRATE CELL — Philip R. White — 629

A CONCEPT OF OPTIMAL NUTRITION — W. A. Krehl — 634

SOME RECENT DEVELOPMENTS IN ORAL FEEDINGS FOR OPTIMAL NUTRITION IN BURNS — Curtis P. Artz, Harry S. Soroff, Elinor Pearson, and Robert P. Hummel — 642

THE DIAGNOSIS OF MALNUTRITION IN WELL-NOURISHED COMMUNITIES — A. M. Thomson — 647

THE RELATIONSHIP BETWEEN POTASSIUM UTILIZATION AND NITROGEN BALANCE — Laurence E. Frazier, Randolph H. Hughes, and Paul R. Cannon — 655

OPTIMAL NUTRITION CORRELATED WITH NITROGEN RETENTION — James B. Allison — 662

POSTABSORPTIVE UNDULATIONS AND OSCILLATIONS IN BLOOD GLUCOSE — George E. Anderson, Robert W. Hillman, Izak F. A. Van Elk, and A. John Perfetto — 673

EDITORIAL: ANTIBIOTICS PLUS? — Charles S. Davidson — 687

REVIEWS OF RECENT BOOKS — 689

ABSTRACTS OF CURRENT LITERATURE: ENERGY REQUIREMENTS IN MAN; NUTRITION PROJECTS AND SURVEYS; PYRIDOXINE; THE SPRUE SYNDROME; CARBOHYDRATE METABOLISM; NEW STUDIES ON SERUM LIPIDS; ITEMS OF GENERAL INTEREST — 691

TABLE OF CONTENTS, VOLUME 4 — 709

INDEX, VOLUME 4 — 713

Author Index to Volume 4

Adams, Raymond D., 346
Albanese, Anthony A., 161
Albrecht, A., 269
Allison, James B., 662
Anderson, George E., 673
Artz, Curtis P., 642

Baron, Harry, 254
Bean, William B., 420
Bersohn, I., 117
Beychok, Sherman, 254
Boas, Ernest P., 10
Bodansky, Oscar, 45, 51
Boek, Jean K., 239
Boozayaangool, Rith, 280
Boyd, Linn J., 124
Brock, J. F., 286
Broquist, H. P., 269
Brown, Frederick R., 285
Burke, Bertha S., 37, 231

Cannon, Paul R., 655
Carol, Ruth, 1
Chalmers, Thomas C., 224
Chow, Bacon F., 142, 147, 434, 440
Christenson, W. N., 609
Conn, Jerome W., 523
Cott, Cora L., 275
Coursin, David Baird, 354
Coyne, Richard, 61

Darby, William J., 291, 309
Daum, Kate A., 420
Davidson, Charles S., 687
Davies, J. N. P., 539
Day, Paul L., 386
Dinning, James S., 386
Duncan, G. D., 408

Eales, L., 529
Edwards, D. A. W., 35
Epstein, Frederick H., 1, 10
Esselbaugh, Nettie C., 261

Follis, Richard H., 107
Forbes, Clare E., 178
Ford, W. J. A., 625
Frazier, Laurence E., 655
Friskey, Roger W., 285

Gibbens, Janis, 151
Gilbert, Jack P., 134, 142
Glass, George B. Jerzy, 124
Goldbloom, A. Allen, 124
Goldsmith, Grace A., 151
Gordon, Harry H., 391
Grace, William J., 609
Grasbeck, Ralph, 147
Greenberg, Louis D., 311, 318
Guggenheim, K., 71
Gupta, Om P., 246
György, Paul, 313

Hansen, J. D. L., 286
Hard, Margaret McGregor, 261
Harris, Philip L., 402
Harvey, C. C., 408
Helliger, Andre E., 440
Henley, Elaine D., 609
Higgons, Reginald A., 161
Hillman, Robert W., 603, 673
Hopp, Ralph L., 625
Horonick, Andrew, 434
Horwitt, M. K., 408
Howe, E. E., 286
Hughes, Randolph H., 655
Hummel, Robert P., 642
Hyde, Gertrude M., 161

Iber, Frank L., 224

Joelson, Robert H., 279
Johnson, Mary Louise, 37, 231
Johnson, Robert D., 523
Johnson, Robert E., 466
Jolliffe, Norman, 580
Jukes, T. H., 269

Kark, Robert M., 463
Katchman, Arthur, 254
Kemp, Robert L., 61
Keys, Ancel, 74
Kinsell, Laurance W., 285
Kleiner, Israel S., 254
Krause, R. F., 68
Krehl, W. A., 634
Kridakara, Od, 280
Kushner, Daniel S., 561

Laughton, Roger, 124
Lowe, K. G., 486
Lubin, Robert, 420

Mann, George V., 76
Mason, Karl E., 402
Mayer, Jean, 37, 169, 231
McHenry, E. W., 364
Merrill, Arthur J., 497
Metcoff, Jack, 543
Meyer, Margaret E., 246
Michaels, George D., 285
Mickelsen, Olaf, 291
Miller, A. T., 619
Miller, O. Neal, 151
Mitra, Kamakhya Prasad, 169
Morgan, Mary C., 134

Nitowsky, Harold M., 391, 397

O'Connor, S. J., 625
Okuda, Kunio, 142, 147, 434, 440
Orto, Louise, 161

Patterson, E. L., 269
Pearson, Elinor, 642
Perfetto, A. John, 673
Plough, Irvin C., 224

Randall, Henry T., 45, 51
Reisner, Edward H., 134
Rich, Marilyn, 124
Rinehart, James F., 318
Robinson, Corinne H., 288
Rosen, Sidney, 124
Rosenblum, Charles, 134
Roy, Purnima, 169

Saltza, M. H. von, 269
Sanders, P. L., 68
Sargent, Frederick, 466
Schaefer, Arnold E., 291
Schwartz, Morton K., 45, 51
Sebrell, William H., 582
Shaw, James H., 246
Shipman, Margaret E., 224
Shuman, Charles R., 61
Simpson, Rita, 1, 10
Soroff, Harry S., 642
Squire, John R., 509
Stokstad, E. L. R., 269
Sure, Barnett, 211

Thomas, Barbara M., 619
Thomson, A. M., 647
Tildon, J. Tyson, 397
Tower, Donald B., 329

Unglaub, Walter G., 151

Vague, Jean, 20
Valtin, H., 486
Van Elk, Izak F. A., 673
Victor, Maurice, 346
Vilter, Richard W., 378
Volker, J. F., 280

Wachstein, M., 369
Waife, S. O., 176, 580
Wayburne, S., 117
White, Philip R., 629
Williams, William L., 147
Wilson, W. C., 408
Wohl, Michael G., 61
Wolff, Harold G., 609
Woodruff, Calvin W., 597
Wynne, E. Staten, 275

Yuktananda, Isra, 280

Zimmerman, Hyman J., 482

Subject Index to Volume 4

(A) *Abstracts* (E) *Editorial* (L) *Letter to the Editor*

Abstracts, grouped by subject:
  Alcohol and Nutrition, 302
  Anemia, Clinical Observations, 94
  Arteriosclerosis: Nutritional Considerations, 447
  Carbohydrate Metabolism, 698
  Cardiovascular Disease, Sodium and, 191
  Energy Requirements in Man, 691
  Fluorine, Essential Trace Element? 200
  Growth-Promoting Factors. 98
  Iodine Deficiency, 202
  Iron Metabolism, 452
  Items of General Interest, 83, 102, 203, 307, 460, 703
  Kwashiorkor and Protein Malnutrition, 298
  Metabolic Aspects of Stress, 101
  Milk and Lactation, 305
  Niacin Requirements and Metabolism, 591
  Nutrition and the Gastrointestinal Tract, 594
  Nutrition and Small Intestine Function, 92
  Nutrition and Pregnancy, 449
  Nutritional Projects and Surveys, 693
    methods and results, 83
  Pancreas, and Lipids, 456
  Peptic Ulcer, Dietary Management of, 297
  Pediatric Nutrition, Problems in, 86
  Pernicious Anemia and Vitamin B_{12}, 458
  Protein Nutrition, Special Aspects of, 188
  Pyridoxine
  Rickets, Vitamin D, and Calcium, 194
  Serum Lipids, New Studies on
  Sodium and Cardiovascular Disease, 191
  Sprue Syndrome, 697,
  Steatorrhea, 89
  Thiamine Metabolism, 199
  Thinness and Undernutrition, 189
  Vitamin C Intake, Serum Levels, Actions, 306
  Vitamin E, Observations on, 99
  Vitamin K, Action of, 455
Acrodynia, 314
Albuminuria, 470
Amino acid(s) (see also individual acids)
  balance, 664
  and carbohydrate interrelation, 334
  enrichment of foods, 214
  and the heart, 110
  in kwashiorkor, 286
  in plasma, effect of food on, 275ff
  and protein metabolism, 333
  and vitamins, 286
Anemia(s)
  clinical observations, 94 (A)
  effect on renal function and scruvy, 530, 436
  intrinsic factor preparations for, 135, 143, 147ff
  iron tolerance tests in, 609ff
  megaloblastic (see pernicious anemia)
  microcytic, 325
    and vitamin B_6, 315
  pernicious, and vitamin B_{12}, 458 (A), 137ff
    anti-pernicious anemia products, 139, 147ff
    differentiation from sprue, 137
    and pyridoxine, 319
    urinary tests in, 135ff
Antibiotics plus, 687 (E)
Arginine in kwashiorkor, 286
Ascorbic acid
  actions, intakes, serum levels of, 306 (A)
  and burns, 643
  and nutritional status of adolescents, 261
  renal function and, 529ff
Asparagine and metabolic abnormalities, 338
Atherosclerosis
  android obesity and, 29
  aortic, 203
  calcification as diagnostic criteria, 12
  cholesterol and, 121
  and ethnic origins, 10ff
  etiology of, 1
  and fat intake, 11
  and lipid metabolism, 10
  nutritional considerations, 447 (A)
  and obesity, 14, 21, 29
  and vitamin B_6, 315, 318ff, 323

"Beriberi" heart, 111
Biotin and the heart, 112
Blood (see also Anemia)
  glucose
    effect of dextran on, 279
    sorbitol and, 61ff
  levels and pyridoxal phosphate, 379
    of vitamin B_{12} in pregnancy, 440
  pyruvate level, 619
  and urine, analysis, 410
Book Reviews:
  Bettmann, O. L.: *A Pictorial History of Medicine*, 690
  Betz, H., and Roulet, F. C. (Eds.): *Transactions of the 4th Meeting of the International Society of Geographical Pathology*, 186
  Byrd, O. E.: *Nutrition Sourcebook*, 81
  Cantarow, A., and Trumper, M.: *Clinical Biochemistry*, 81
  Conrad, M. L.: *Allergy Cooking*, 295
  Elkinton, J. R., and Danowski, T. S.: *The Body Fluids—Basic Physiology and Practical Therapeutics*, 81

Harris, R. S., Marrian, G. F., and Thimann, K. V. (Eds.): *Vitamins and Hormones. Advances in Research and Applications, Vol. XIII*, 295
Holman, R. T., Lundberg, W. O., and Malkin, T.: *Progress in the Chemistry of Fats and other Lipids, Vol. III*, 446
International Society of Geographical Pathologists: *Transactions of the 5th Meeting*, 590
Jelliffe, D. B.: *Infant Nutrition in the Subtropics and Tropics*, 589
Lemkau, P. V.: *Mental Hygiene in Public Health*, (ed. 2), 185
Mrak, E. M., and Stewart G. F. (Eds.): *Advances in Food Research*, Vol. VI, 186
Martin, G. J.: *Ion Exchange and Adsorption Agents in Medicine—The Concept of Intestinal Binomics*, 295
McElroy, W. D., and Glass, H. Bentley (Eds.): *A Symposium on Amino Acid Metabolism*, 689
Moutier, F., and Cornet, A.: *Les Gastrites*, 187
Pollack, H., and Morse, A. D.: *How to Reduce Surely and Safely*, 590
Rytand, D. A., and Creger, W. (Eds.): *Annual Review of Medicine, Vol. 7*, 446
Schwimmer, M., and Schwimmer, D.: *The Role of Algae and Plankton in Medicine*, 186
Sterling, Julian A.: *The Biliary Tract*, 589
Strachan, C. B.: *The Diabetic's Cookbook*, 690
Swedish Institute for Food Preservation Research: *Proceedings of Symposium on Nutritive Aspects of Preserved Food*, 689
Waterlow, J. C. (Ed.): *Protein Malnutrition*, 296
Werner, S. C. (Ed.): *The Thyroid*, 82
Wishik, S. M.: *Feeding Your Child*, 81
Wohl, M. G., and Goodhart, R. S. (Eds.): *Modern Nutrition in Health and Disease*, 185
Burns, optimal nutrition in, 639, 642ff

Calculous disease, urinary and bilary, 20ff
  and android obesity, 28ff
Calipers for measuring skin-fold thickness, 36
Caloric intake
  activity level, 4
  body build and, 4
  estimation of, 1ff
  of ethnic groups, 2, 11, 169
  expenditure, 37
  and fat intake, 11
  and nitrogen storage in liver disease, 224
  in optimal nutrition, 662
  and physical work, 37ff, 169ff
  and population groups, 1ff
Calories and protein metabolism, 663
Cardiovascular disease, sodium and, 191 (A)
  nutritional deficiency and, 107ff
Carotene (see vitamin A)
Cheilosis, in vitamin A toxicity, 604
Children (see also infants),
  adolescent, nutritional status of, 261
  convulsive seizures and pyridoxine, 346
  dental survey of, in Thailand, 280ff
  nutrition of
    and nervous disorders, 354
    in underdeveloped countries, 219
  obesity in, 37, 231ff, 288
  physical activity and obesity in, 37ff
  renal defense of body composition in, 543ff
  tocopherol
    deficiency in, 397ff
    metabolism, 391ff
    and vitamin B_6 deficiency, 383
Cholesterol
  in (African and European) infants and mothers, 117ff
  in atherosclerosis, 10, 121
  and body build, 6
  and cholesterol esters, 428
  and ethnic origin, 14, 118ff
  high fat intake and, 74ff (L), 285 (L), 14, 120, 464
  high protein diet and, 224
  and liver disease, 120
  low fat diet and, 76
  obesity and, 14
  and sex hormones, 120
  triglyceride and, 285 (L)
  unsaturated fatty acids and, 285 (L), 464
Cirrhosis (see also liver)
  biliary, and vitamin E, 597ff
  and dietary nitrogen intake, 224ff
  and fatty metamorphosis, 321
  sex hormones and, 120
  and vitamin B_6, 120, 318ff
Cobalt (see also Vitamin B_{12}) and the heart, 110
Cocarboxylse (disphosphothiamine), 329
Convulsive seizures and pyridoxine, 329, 340, 346, 347ff, 354, 383
Copper, deficiency, and the heart, 109
Coronary artery disease
  death rate, fat intake and cholesterol, 120
Cortisone
  as antidote for vitamin D toxicity, 570
  effect on calcium metabolism, 570
  in nephrosis, 519ff
Creatinuria in vitamin E deficiency, 600
Cystine-storage disease, 552

Dental caries
  food-nutrient intake, 261
  and gingival health, 280ff
  and low fluoride water supplies, 246ff
  and occlusion, 280ff
  pyridoxine deficiency and, 320
  in Thai children, 280ff
Dextran, effect on blood glucose, 279
Diabetes
  age factor, 243
  android obesity and, 27
  blood sugar variations in, 673ff
  causes of, 30
  dextran and, 279

obesity and, 20
sorbitol and, 61ff
Diet (see also nutrition)
of adolescents, 261
cholesterol level and, 120
corn and pellagra, 151ff
and dental caries, 280ff
and economic status, 239ff
ethnic origin and, 10ff
fiber content in, 289ff
and fluoride content of teeth, 246ff
in glomerulonephritis, 482ff
high protein, 255ff
and cirrhosis, 224ff
and hepatic coma, 224
and low-sodium, 255
preparation of, 254ff
and hypercholesteremia, 14ff
and life span, 240
low-sodium in nephrosis, 514
low fat, 393
and vitamin E deficiency, 599
in nephrosis, 513
in nephrotic edema, 513
and peptic ulcer, 297 (A)
and plasma amino acids, 275
and population, 212ff
and renal function, 466ff, 504ff
and scurvy, 529ff
and schooling, 242
and social characteristics, 239
tocopherol in, 410
Dietary histories and surveys
adolescent children, 261ff
caloric intake, 40, 41
groups, characteristics of, 2ff, 39
standards, 649
techniques, 38, 39, 239
basal metabolic rates and surface area, 5
and lean body mass, 6
"modified" 24 hour, 2ff, 7
nomogram-predicted intake, 2ff
"short method" for calculations, 2
for testing renal function, 466ff
Dietary requirements in optimal nutrition, 625
Diet Therapy
Development and role of a food clinic, 178ff
Fiber in the diet, 288ff

Editorials, 176, 580, 687
Energy (see also caloric intake) requirements in man, 691 (A)
Eosinopenic response to ACTH, 424
Epilepsy, seizures (see convulsive seizures)
Eutrophy, 176 (E)
Exercise, pyruvate levels after, 622

Fat
and caloric intake, 2, 11ff
and cholesterol levels, 14, 74ff (L), 285 (L), 464
and chronic renal failure, 504
and fecal calcium, 55ff
distribution of, and obesity, 35
as sexual characteristic, 23ff, 35
gastrectomized patients, toleration of, 45
intake and coronary artery disease, 1, 13, 120
measurement by skin-fold, 6, 35ff
metabolism in surgical patients, 51ff
triglyceride and cholesterol, 285 (L)
Fatty Acids
lipid levels and, 285 (L)
in milk, 379
triglyceride content, 285 (L)
unsaturated, and blood cholesterol levels, 464
and vitamin B_6, 315, 380
Fiber in diet
increasing and decreasing content, 289
Fluorine and teeth, 200 (A), 246ff, 261
essential trace element? 200 (A)
Food(s) (see also diets, nutrition, specific substances)
algae as extender, 216
calcium sources, 561
and cholesterol levels, 119
clinics, development and role, 176
in coma, 625ff
high carbohydrate and dental caries, 284ff
high protein, 254
intake
of adolescents, 261
and amino acids in plasma, 275ff
low-cost, high protein, 215
low sodium, 254
production and world population, 211ff
and social characteristics, 239

Gastrectomy
fat and mineral metabolism in, 51ff
nitrogen metabolism after, 45ff, 51
steatorrhea after, 51ff
Glomerulonephritis,
nutritional aspects of, 482ff
Glucose
arterial fluctuations of, 683
pyruvate levels after, 619
tissue utilization of, 684
variations in blood, 673ff
venous resurgence of, 680
Glutamic acid
and brain, 334
in convulsive seizures, 338
and liver, 334
Glycine and food intake, 275
Glycosuria, 469
Gout
and chemical uremia, 565
and obesity, 20ff, 28
Growth and optimal nutrition, 630, 639, 647
Growth-promoting factors, 98 (A)

Heart (see also atherosclerosis)
amino acids and, 110

ascorbic acid and, 112
and beriberi, 111
biotin and, 112
cobalt and, 110
copper deficiency and, 109
iron-deficiency and, 109
malnutrition and, 113ff
niacin and, 112
nutrition and, 107ff
pantothenic acid and, 111
potassium deficiency and, 107ff
pteroylglutamic acid and, 112
pyridoxine and, 111ff
sodium, effects on, 109, 254
thiamine and, 110
vitamin E and, 113
vitamins and, 110
Hypercalcemia, 56
chronic, 574
functional renal injury and, 566
idiopathic infantile, 569
Hypokalemia, 501, 523, 526
Hypophosphatasia, 574

Infection and nutrition, 639
Insulin, 3, 104 (A) (see also diabetes)
extrinsic, effect of, on fluctuations, 683
and liposynthesis, 30
speed of peripheral action of, 679
tolerance test, 425
Intrinsic factor preparations
and deficiency of vitamin B_{12}, 128ff
effect of, in absorption of vitamin B_{12}, 147ff
urinary test for assaying, 135
Iodine, deficiency, 202 (A)
Iron (see also anemia)
absorption
from gastrointestinal tract, 609
studies, 610
tolerance test, 609
radioactive, 609
Isonicotinic acid hydrazide and neuritis, 381

Ketonuria, 469
17-Ketosteroid-creatinine ratio, 425
Kidney (see also renal function), 463ff
Kwashiorkor (see also protein malnutrition)
albuminuria and, 539
amino acids in, 286
biochemical changes in, 539
fat changes in kidney and liver and, 540
histidine in, 286
pathologic changes in kidney and, 539
and protein malnutrition, 218, 298 (A)
renal lesions in, 539

Leucine and food intake, 275
Lipid(s)
food habits and, 119
hormonal mechanisms of, 20
metabolism, 15, 20, 330ff
new studies on, 700 (A)
oxidations and tocopherol intake, 408ff
and pancreas, 456 (A)
racial differences and, 119
triglyceride and, 285
Lipoic acid, alpha (see thioctic acid), 269
Lithiasis, therapy of, 567
Liver
and cholesterol levels, 120
disease (see also cirrhosis), 224
function tests, 427
glutamic acid in, 334
nutritional deficiency and, 71
pitressin-inactivation and nutrition, 81
proteins and, 666
uptake of vitamin B_{12}, 124
vitamin A, content of, 68ff
vitamin deficiency and, 69, 71
Lysine
deficiency in wheat proteins, 213
and food intake, 275
supplementation and proteins, 163
-tryptophan protein, 161, 163

Magnesium, deficiency, and the heart, 108
Malnutrition, 639
and chronic liver disease, 120
diagnosis of, 647ff
and the heart, 115
and overpopulation, 211ff
protein and kwashiorkor, 298 (A)
and renal function, 463ff, 529, 548
and thinness, 189 (A)
in well-nourished communities, 647ff
Metabolism
abnormalities of, 338, 369
basal rates in dietary histories, 3ff
calcium, and the kidney, 561ff, 502
carbohydrate, 334, 364, 619, 628 (A)
-glucose, 673ff
cellular of cystine, disorder of, 552
cerebral nervous tissue, 334
in coma, 625ff
fat, (ty), 364
acid in, 331
and kwashiorkor, 540
and mineral, 51ff
iron, 452 (A)
liver cell, low protein and, 299 (A)
neuronal
glutamic acid in, 334
and vitamin B complex, 329ff
and vitamin B_6 354ff
of newer vitamins, 309
nitrogen, 45ff, 655ff
in gastrectomized patients, 51ff
and obesity, 176 (E)
optimal nutrition and, 640
in pregnancy, 381ff

pantothenic acid, 420
protein and amino acid, 333ff, 364ff, 662ff
protein-potassium, 655ff
pyridoxine in, 323ff, 341, 372, 378
pyridoxine-tryptophan, 332
pyruvate disphosphi-thiamine in, 329
sodium in chronic renal failure, 499
and sorbitol, 666
test for, 424
tocopherol, 391, 397, 402, 408
tryptophan, 323, 332
of vitamin B_6, 364ff, 378ff
Milk and lactation, 305 (A)
Muscle dystrophy,
and α-tocohydroquinone, 402ff
and vitamin deficiency, 386ff

Nephrolithiasis, 560
Nephropathy, 575
Nephrosis
clinical appearance, 510
cortisone therapy, 519
depletion of body n²trogen in, 510
dietary measures for control of fluid, 513ff
Neuritis, pyridoxine and, 381
Niacin requirements and metabolism, 591 (A)
Nitrogen
balance, 662ff
depletion
in burns, 643
in nephrosis, 510
metabolism in surgical patients, 45ff
and potassium utilization, 655
retention and optimal nutrition, 662ff
storage in cirrhosis, 224
Nutrition (see also under specific nutrients)
and alcohol, 203 (A)
and amino acids, 110, 214 (A), 631
deficiency and nephrosis, 510
and dental caries, 280
in gastrectomized patients, 45, 51
and gastrointestinal tract, 594 (A)
and glomerulonephritis, acute, 482ff
and growth, 647
and the heart, 107ff
and inorganic elements, 107ff
of the isolated cell, 629
and the liver, 71ff
and mortality, 647
and the nephrotic syndrome in adults, 509ff
optimal level in burns, 643
pediatric, 86 (A)
and pregnancy, 449 (A)
projects and surveys, 83 (A), 693 (A)
in prolonged coma, 625
and renal function, 463, 497ff
and small intestine function, 92 (A)
and vitamins, 110
Nutrition Briefs, 182, 293, 586
Nutrition News, 78, 181, 292, 444, 585

Nutritional Quotes, 80, 183, 294, 587

Obese, are they metabolically different? 176 (E)
Obesity
android, 24ff
and atherosclerosis, 11, 14, 21, 29
and biliary calculous disease, 28
caloric intake and expenditure in, 37ff
in children, 231ff
diabetes and, 20ff, 27
duration of, 237
and emotional factors, 640
estimation of, by skin-fold, 35
and gout, 28
growth and, 39
gynoid, 24, 27, 30
hyperandroid, 23
hypergynoid, 23
masculine differentiation, index, 20ff
and menarche, 39
and metabolism, 176 (E)
natural history of, 237
physical activity and, 40
physical maturation and, 39, 42
prevalence of, 231ff
protein anabolism and, 31
pyruvate metabolism in, 619
seasonal effects on, 235
and uric calculous disease, 20
Obituary
James Fleece Rinehart, 311
Harold Russel Sandstead, 291
Optimal nutrition, (symposium) 628ff, 634ff, 642ff
amino acid balance and, 664
in burns, 639, 642ff
dietary requirements in, 635
in growth, 630, 639, 647
and health, 649
infection and, 639
and isolated cells, 628
and mortality, 647
and nitrogen retention, 662ff
and proteins, 638
and stress, 636
and tissue culture studies, 630
Osteomalacia and late rickets, 570

Pancreas and lipids (see also diabetes), 456 (A)
Pantothenic acid and the heart, 111
metabolism of, 420
Para-aminobenzoic acid acetylation, 424
Pellagra
and lime-treated and untreated corn, 151ff
niacin-tryptophan relationship in, 153
nicotinic acid (amide) and, 314
vitamin B_2 and, 313
and vitamin B complex deficiency, 380
Pentosuria and vitamin E deficiency, 600
Pitressins and nutritional deficiency of liver, 71ff
Potassium (see also renal function)

in chronic renal failure, 499, 501
deficiency of, and
kaliopenic nephropathy, 464, 523
and the heart, 107ff
in surgery, 51ff
Pregnancy
abnormalities of tryptophan metabolism, 381
and nutrition, 638
and pyridoxine intake, 381
vitamin B_{12} levels in, 440
vitamin B_6 metabolism in, 369
Protein(s)
and burns, 639, 642
and calorie consumption in nephrotic patient, 510, 515, 520
catabolism and chronic uremia, 502ff
deficiency in geriatrics, 640
food yeasts as supplements, 215
lysine-tryptophan content of, 161ff
and malnutrition, 212, 286
metabolism, 662ff
nutrition, special aspects of, 188 (A)
optimal, 632
plasma, 667
in rhesus monkeys, 318
serum tests, 427
and sodium chloride in diet, 209
sources for children in underdeveloped countries, 219
synthesis, 334
Prothrombin, activity, 428
Pteroylglutamic acid and the heart, 112
Public health, nutrition in, 647ff
Pyridoxal phosphate (see pyridoxine), 336, 381
Pyridoxine (al) (amine) (vitamin B_6), 316, 378ff, 696(A)
absorption, 378
in amino acid metabolism, 334ff
and arteriosclerotic changes, 315, 320
and blood levels, 379
and cerebral metabolism, 380
and cirrhosis, 321
in convulsive seizures, 337ff, 354, 383
deficiency in monkeys, 346ff, 318ff
and degenerative changes, 369, 376
and dental caries, 320
desoxypyridoxine-induced, 331
enzymatic activity, 319, 323, 365
and the heart, 111
history of, 313
metabolism of, 318, 327, 346, 354, 364, 378
in microcytic anemia, 315
in milk, 356, 379
muscular dystrophy and, 386
in neuritis, 381
neurochemical aspects of, 329ff, 346ff
in protein synthesis, 334ff
and pregnancy, 369, 381
and *streptococcus faecalis* R, 315

Renal function (the kidneys), 463ff
body fluids, regulation of, 543ff
calcium and, 561ff
absorption, 561ff
cortisone and, 570
in children, 543ff
chronic failure of, 497ff
in health, 466ff
and kwashiorkor, 539ff
lesions, 525ff
metabolism, 568
nutritional management and, 497ff
in scurvy, 529ff
syndromes, 521, 552, 554, 569
vitamin D and, 570ff
Riboflavin (vitamin B_2)
and the heart, 112
and pellagra, 314
in rat acrodynia, 314
Rickets, vitamin D, calcium and, 194 (A)

Scurvy (see also ascorbic acid), renal lesions in, 529ff
Sea-salt as source of fluoride, 250ff
Sex hormones, balance of, and liver disease, 121
Skin, in vitamin A toxicity, 604
Skin-fold, measurement, 6, 35
Sodium (see also renal function)
and cardiovascular disease, 191(A)
in chronic renal failure, 500
content of food, 254
and the heart, 109
intake and the kidney, 464
Sorbital
in diabetes mellitus, 61ff
laxative effects of, 66
metabolic effects of, 66
Sprue
and anemia, 137
syndrome, 693 (A)
Starvation and the heart, 115
Steatorrhea, 89 (A)
and normal fat metabolism, 45, 137
Streptococcus foecalis and pyridoxine, 315
Stress and homeostasis, 636
Stress, metabolic aspects of, 101 (A)

Thiamine, (vitamin B_1), 105 (A), 313
and acrodynia, 314
and the heart, 110
lack of, in visible edema, 71
metabolism 199 (A)
Thiobarbituric acid, test, 417
Thioctic acid, urinary excretion of, 269ff
α-Tocopherol (see Vitamin E)
effects of limited intake, 408ff
in infants and children, 391ff
plasma, 394, 411
α-Tocohydroquinone and muscle dystrophy, 402ff
Transaminase, in vitamin B deficiencies, 365
Tribute to R. R. Williams, 580 (E)
Tri-glyceride, synthetic, fatty content of, 285 (L)
Tyrosine in kwashiorkor, 286

Tryptophan-Dl, 369 (L)
and food intake, 276
load test, 371
-lysine and proteins, 161
metabolism in pregnancy, 369, 381
and proteins, 161
synthesis of niacin from, 309
in vitamin B_6 deficiency, 276, 316
and xanthurenic acid in urine, 369, 379, 381
Tumors, protein metabolism and, 668

Uric calculous disease and obesity, 20
Urinary excretions,
analysis and blood, 410
constituents and hemoglobin valves, 263
tests
diazo reaction, 371
tryptophan load test, 371
for vitamin B_{12} absorption, 134ff, 142ff, 147ff
of thioctic acid, 269ff
of xanthurenic acid, 316

Vitamins (see under specific substance)
and burns, 643
and the heart, 110
as metabolities, 310
as proenzymes, 316
syntheses of, in man, 309
Vitamin A
and the heart, 112
and the liver, 68ff
synthesis of, in man, 309
toxicity, 603ff
Vitamin B complex, in neuronal metabolism, 329ff
Vitamin B_1 (see thiamine)
Vitamin B_2 (see riboflavin)
Vitamin B_4, deficiency, in acrodynia, 314
Vitamin B_6 (see pyridoxine)
Vitamin B_{12}
absorption, 124, 134ff, 142ff, 434
age and, 124
elixir of, 434ff
gastric secretory function and, 127
and the heart, 112
in human nutrition, 309, 434, 440
intestinal absorption of, 124ff
and age, 132
and hepatic intake, 124ff
radio-active effect of intrinsic factor preparation, 124
serum level of, in pregnancy, 440ff
urinary test as index, 134ff, 142ff, 147, 436
Vitamin C (see ascorbic acid)
Vitamin D, in renal function, 505, 570ff
Vitamin E (see also tocopherol)
cystine deficiency and, 380
deficiency, 597ff
and dietary hepatic necrosis, 389
and the heart, 113
in infants, 391
and muscular dystrophy, 387
observations on, 99 (A)
and transaminase, 376
Vitamin K, action of, 455 (A)
synthesis in man, 309

Wounds, healing, and nutrition, 630

Xanthuric acid, urinary, 380
in diabetes, 381
in pregnancy, 381
and pyridoxine, 381
and tryptophan, 316, 332, 369

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The American Journal of Clinical Nutrition is published bimonthly by The American Journal of Clinical Nutrition, Inc., 49 West 45th Street, New York 36, N. Y. Yearly subscription, $8.00 U.S.A.; $8.50 Canada, $9.00 foreign. Single Numbers, $1.75; foreign, $2.00. Symposium Numbers, $3.00. Entered as second class matter April 28, 1955 at the Post Office, Easton, Pa. and on June 23, 1955 at the Post Office, New York, N. Y. November–December 1956—Volume 4, No. 6.

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MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th Street, New York 36, N. Y.

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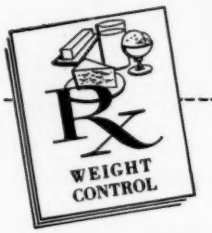

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1. Watt, B.K., and Merrill, A.L.: Composition of Foods —Raw, Processed, Prepared—Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.

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Discussion — The "well-regulated" diabetic may still fall prey to the degenerative complications of the disease, since it is not enough merely to guard against ketosis or hypoglycemic reactions. In order to preserve protein balance, it is necessary also to guard against a drop in blood sugar so low as to stimulate hepatic glyconeogenesis, lest the alimentary canal be unable to absorb enough nitrogen to maintain protein balance. Therapy calls for a high protein diet amply fortified by vitamins and (at least in the beginning) by the digestive enzymes of the pancreas, in order to stimulate protein recovery and to enable the lipotropic action of the protein to become fully manifest.

Conclusions and Summary—A group of 25 diabetics treated with a special high protein diet, oral pancreatic enzymes (Entozyme), and careful regulation of their insulin dosage so that neither excessive hyperglycemia nor hypoglycemia occurred showed significant symptomatic improvement. In most cases there was not only a decline in the serum cholesterol levels, but also a reduction in insulin requirements.

It is suggested that this improvement is due to redressing the nitrogen balance and making available the lipotropic activity of protein, as well as other intrinsic factors essential to normal tissue metabolism.

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*Lowenstein, B. E.: The Value of Entozyme® in the Clinical Management of Diabetes Mellitus: Preliminary Report. American Pract., September, 1956.

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1. Dieckmann, W. J., and Priddle, H. D.: Anemia of Pregnancy Treated with Molybdenum-Iron Complex, Am. J. Obst. & Gynec. 57:541, (March) 1949.
2. Neary, E. R.: Am. J. Med. Sc. 212:76 (July) 1946.
3. Kelly, H. T.: Pennsylvania M. J. 51:999 (June) 1948.

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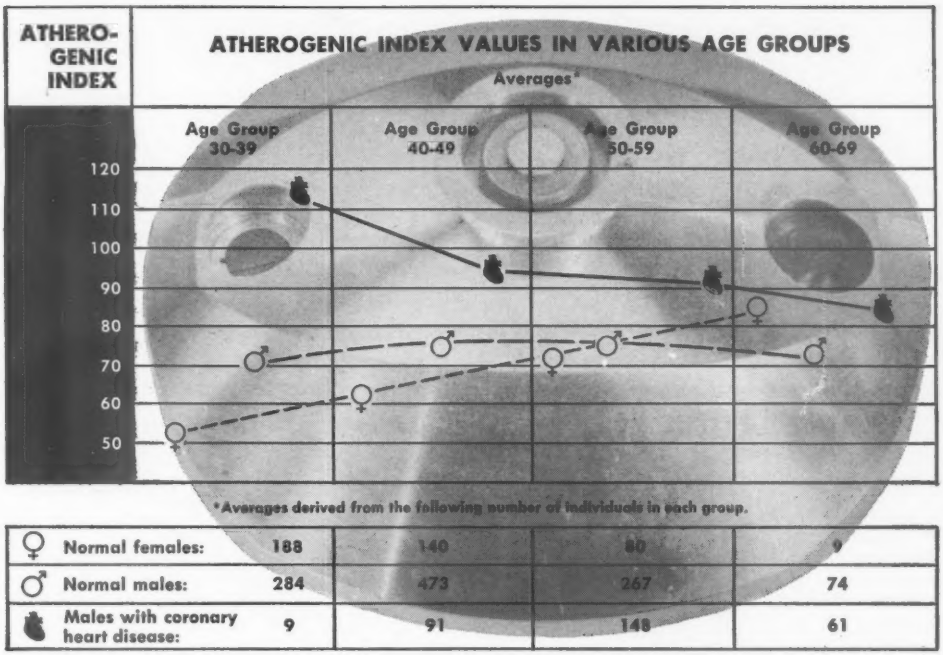

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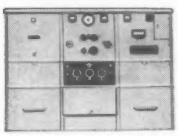

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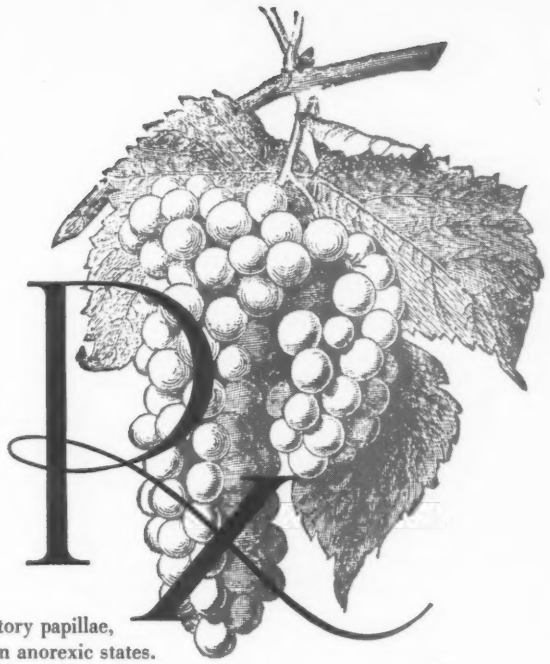

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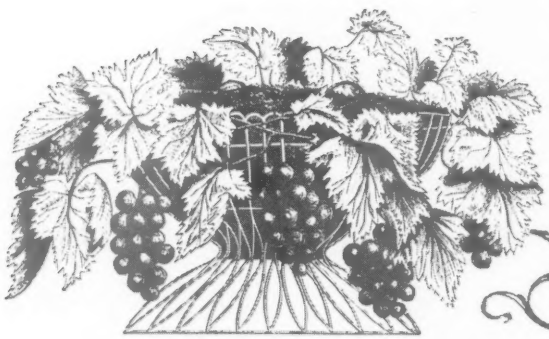

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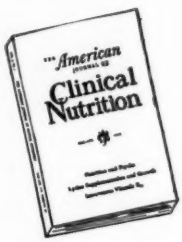

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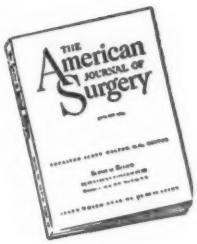

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Advertisers Index

NOV.–DEC. 1956

*American Bakers Association xxiv

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*Ayerst Laboratories . . . .viii, ix, *Inside Back Cover*

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*J. B. Roerig . . . . . *Back Cover*

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*The Wander Co. (Ovaltine) iv

*White Laboratories, Inc . . . . . ii, xiv, xv

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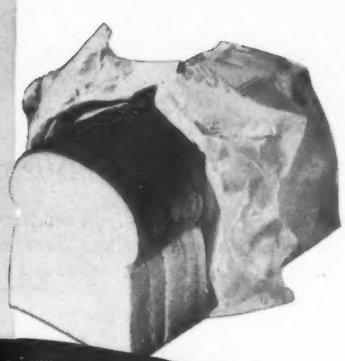

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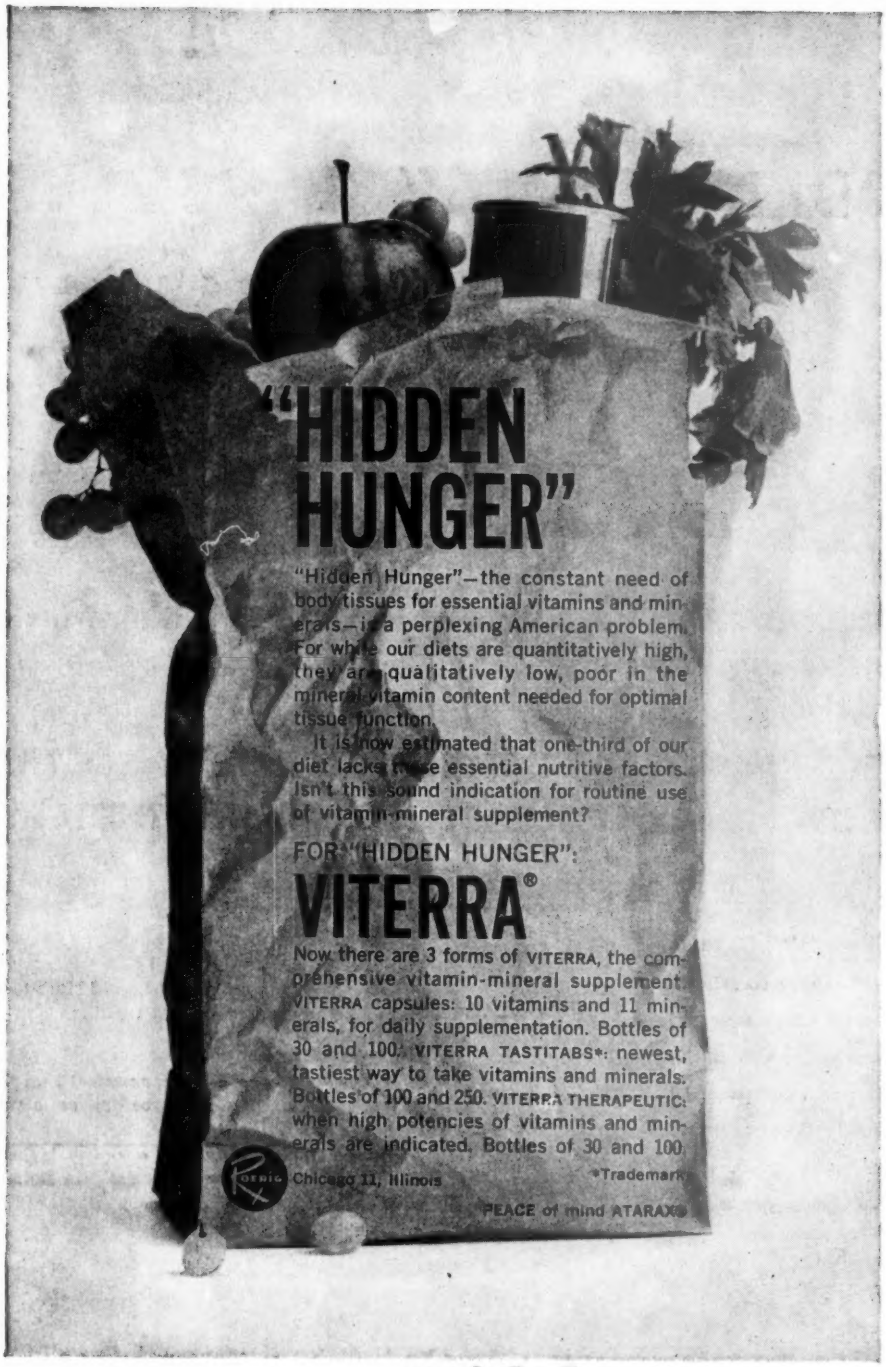
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